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BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 9 1961

"EARLY" EXCHANGE TRANSFUSION

BY

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"Early" exchange transfusion is the accepted treatment in severe haemolytic disease of the newborn, but the definition of early is rarely precise. In the most severely affected infants—those very anaemic and in congestive heart failure at birth—exchange transfusion is urgently required and should be undertaken within a few minutes. In such cases the immediate benefit results from the lowering of venous pressure and the raising of the haemoglobin level. In other cases the chief purpose of exchange transfusion is to remove "sensitized" erythrocytes from the infant, and to replace them with donor cells that will not be affected by the antibody concerned. At the completion of exchange transfusion at least 80% of the circulating red cells should be donor cells having a normal life-span. Thus haemolysis is reduced and the risk that jaundice or anaemia will develop is minimized.

In the majority of infants exchange transfusion is not urgently required and a delay of some hours may be advantageous in enabling the infant to recover from distress associated with delivery. However, during the delay red cells are being destroyed and the resulting bilirubin accumulates because the capacity of the liver to excrete bilirubin is greatly reduced in the newborn infant (Billing *et al.*, 1954).

These factors must be taken into account in choosing the time for exchange transfusion, and during the trial of exchange transfusion *versus* simple transfusion in haemolytic disease of the newborn (Mollison and Walker, 1952) the rules required that exchange transfusion, if selected, should be undertaken within nine hours of birth. After this trial was completed we continued to perform exchange transfusion within this time limit whenever possible, but in recent years we have been prepared to delay transfusion up to about 16 hours provided that the infant's cord haemoglobin value was higher than 11.5 g./100 ml.—that is, the infant was not severely affected.

The purpose of the present study is to review this new policy in the light of experience and to judge whether it is justified.

Material and Method

In the years 1958, 1959, and 1960 80 infants born in hospitals and selected for exchange transfusion on the basis of cord blood values (Walker, 1959) were treated between 9 and 24 hours of life, 67 between 9 and 16 hours. Of these infants, 76 had cord haemoglobin values greater than 11.5 g./100 ml. and four had values between 7.4 and 11.5 g./100 ml. Some infants were born in "outside" hospitals and transferred to Newcastle for treatment, and this caused delay. However, their inclusion is thought to be justified, for any effect produced would be to disfavour later treatment. In fact, their exclusion does not materially affect the results. During the same period 126 additional infants with cord haemoglobin values greater than 11.5 g./100 ml. were selected for exchange transfusion and treated within one to nine hours of birth.

The usual factor determining the age at which exchange transfusion was performed was the time of day when birth occurred. Thus 80% of infants treated between 9 and 24 hours but only 14% of those treated between one and nine hours were born between 7 p.m. and 3 a.m. Exclusion of the exceptions does not alter the findings significantly.

Although the need for and time of exchange transfusion were decided on the cord-blood results it is appreciated that some "selection" may have occurred. Thus if the cord haemoglobin value was only a little above 11.5 g./100 ml., or if early clinical evidence of disease was present, exchange transfusion was probably performed earlier.

In considering the results we sought to avoid bias due to "selection" by a system of "paired cases." Each infant who had been treated between 9 and 24 hours was "paired" with regard to birth weight, cord haemoglobin, and cord bilirubin level with an infant treated earlier. Four pairs with cord haemoglobin values below 11.5 g./100 ml. were included.

Fifty infants with cord haemoglobin values greater than 11.5 g./100 ml. but who were treated in the first nine hours of life were not paired. That the time of exchange transfusion may have been advanced in some of these cases is suggested by our observation that in 46% of them jaundice occurred within the first eight hours of life, whereas this was true for only 35% of both groups of paired cases. With regard to the cord haemoglobin value, too, there is a difference, as shown in Table I.

TABLE I.—*Distribution of Cord Haemoglobin Value for "Paired" and "Unpaired" Cases in Relation to Age at Exchange Transfusion*

	Cord Haemoglobin (g./100 ml.)			
	7·4–11·5	11·6–14	14–15	Over 15
Paired cases treated after 9 hours	5%	24%	36%	35%
Paired cases treated before 9 hours	5%	25%	32%	38%
Unpaired cases treated before 9 hours	4%	58%	36%	2%

A large proportion of unpaired cases had relatively low cord haemoglobin values and only one had a value over 15 g./100 ml., a level above which bilirubin estimation would be needed before deciding on the need for exchange transfusion. This suggests that where the cord haemoglobin value was relatively low and exchange transfusion clearly indicated there was a tendency to proceed with this within nine hours of birth.

We consider that the pairing of cases has largely eliminated errors due to selection, for close correspondence between each pair was achieved for birth weight, cord haemoglobin, and cord bilirubin values (Table I and Fig. 1).

The average weight of infants treated after nine hours was 2½ oz. (70 g.) less than that of infants treated earlier. In 58 pairs the difference in weight was 8 oz. (227 g.) or less, and differences greater than this were confined to babies with a birth weight of over 6 lb. (2,720 g.). In fact, all but eight of these weighed over 7 lb. (3,175 g.).

The average cord bilirubin value of infants treated after nine hours was 0.05 mg./100 ml. lower than

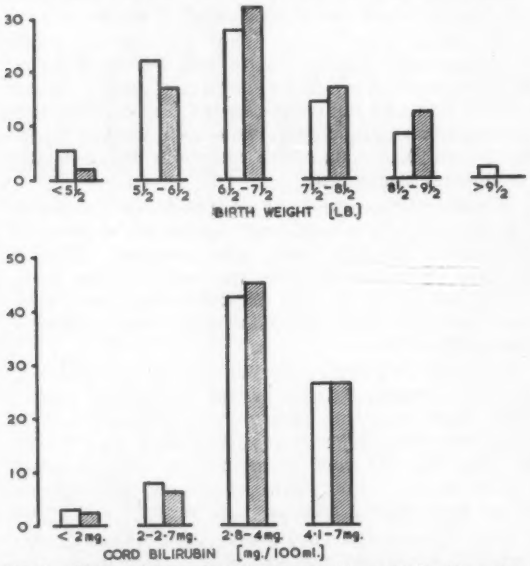

FIG. 1.—Birth weight and cord haemoglobin and bilirubin values in 80 pairs of cases receiving exchange transfusion before (white columns) or after (hatched columns) nine hours.

that of infants treated earlier. All but six pairs had cord bilirubin levels within 0.5 mg./100 ml. Greater differences were restricted to patients with relatively mild disease, the biggest difference being 1.8 mg./100 ml., which occurred in a pair of infants each of whom had a cord haemoglobin value of 15.5 g./100 ml.

The average cord haemoglobin value of infants treated after nine hours was 0.05 g./100 ml. higher than of those treated earlier. In all but 10 pairs the cord haemoglobin value of each pair corresponded within 1.5 g./100 ml. Greater differences, the greatest being 3 g./100 ml., were confined to relatively mildly affected infants. In the group treated early there were six infants in whom the cord haemoglobin value had not been determined but who corresponded with regard to both weight and cord bilirubin.

Sex was not taken into account when the selection of pairs was made, but the distribution was similar in the two groups, being equal in the cases treated before nine hours and 37 males to 43 females in the group treated after this time.

The age at which exchange transfusion was performed is shown in Fig. 2. Otherwise the method and details of exchange transfusion were the same for both groups

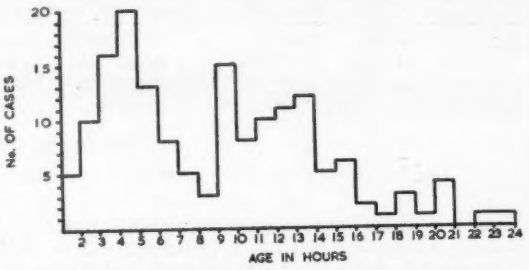

FIG. 2.—Age of infants at time of exchange transfusion.

of infants: 76 in each group receiving an exchange transfusion of over 70 ml./lb. (154 ml./kg.), the remainder receiving between 60 and 70 ml./lb. (132 and 154 ml./kg.).

Any differences that can be demonstrated between the two groups can probably be attributed to the effect of age at exchange transfusion, for there is no real difference with regard to the other factors most likely to influence response to treatment—namely, birth weight, cord haemoglobin level, cord bilirubin value, sex, and method of exchange transfusion.

The two groups have been compared with regard to the time of onset and severity of jaundice, the bilirubin level after exchange transfusion, the need for subsequent transfusion, and the final result.

Results

Jaundice After Exchange Transfusion.—The maximal degree of jaundice in relation to the time at which exchange transfusion was performed is shown in Table II. Sixty-seven of the infants treated in the first nine hours of life developed jaundice, but this was so for 75 of those treated later. The frequency of mild and severe jaundice was the same in both groups, but moderate degrees of jaundice were more common in the group treated after nine hours. The development of jaundice within the first eight hours of life was not

TABLE II.—*Age at Exchange Transfusion in Relation to Subsequent Maximal Jaundice*

Maximal Jaundice after Transfusion	Time of Exchange Transfusion	
	1–9 Hours No. of Cases	9–24 Hours No. of Cases
Nil	13	5
Mild	25	21
Moderate	24	35
Severe	12	14
Very severe	6	5
Total cases	80	80

related to the age at which exchange transfusion was performed but was probably determined by factors already present at birth. However, jaundice developed between 9 and 24 hours more frequently in infants where later exchange transfusion was carried out. Thus jaundice was present on the first day in 68 of the infants treated after nine hours but in 55 treated before this time. On the other hand, jaundice developed between one and three days in 12 infants treated before nine hours but in only seven treated later. It would therefore

seem that early exchange transfusion may delay the onset of jaundice in some infants and prevent it altogether in others. On the other hand, exchange transfusion in the period one to nine hours was not more effective than exchange transfusion between 9 and 16 hours in preventing severe jaundice. Bilirubin estimations were performed only in infants who developed moderately severe jaundice. The maximal levels reached in relation to the age at transfusion are shown in Table III. Bilirubin levels of over 15 mg./100 ml. were observed in 16 infants treated between one and nine hours but in 18 infants transfused after this time.

TABLE III.—*Age at Exchange Transfusion in Relation to Subsequent Maximum Recorded Bilirubin Level*

Maximum Recorded Bilirubin Level	Time of Exchange Transfusion	
	1–9 Hours No. of Cases	9–24 Hours No. of Cases
0–10 mg./100 ml. ..	5	3
10·1–15 ,, ..	9	5
15·1–20 ,, ..	9	9
20·1–25 ,, ..	5	6
>25 ,, ..	2	3
Total cases ..	30	26

Need for Subsequent Treatment.—During the years concerned repeated exchange transfusion was carried out if the bilirubin level reached approximately 25 mg./100 ml. Five infants in each group required two exchange transfusions, while an additional two in each group required more: three received three exchange transfusions and one four. This latter infant had been treated initially at six hours. Of the 14 cases requiring repeated exchange transfusion, no two constituted a corresponding pair. Seventeen infants received simple transfusion for the relief of anaemia because the haemoglobin level fell to approximately 7.4 g./100 ml. within the first six weeks of life. Twelve of these had been treated initially in the first nine hours of life and five had received later exchange transfusion.

Effect of Treatment.—Deterioration of the infant's clinical condition during exchange transfusion occurred in six infants transfused within one to nine hours but in only three treated after this time. The condition during exchange transfusion was recorded as good in 46 and satisfactory in 24 infants treated early, and as good in 51 and satisfactory in 25 treated later. All the infants treated by exchange transfusion between 9 and 24 hours survived, but two deaths occurred in the cases treated between one and nine hours, although neither was attributed to haemolytic disease of the newborn. Both occurred from congenital heart disease.

Discussion

Antenatal prediction of haemolytic disease of the newborn is sought in order that affected infants may be born in hospitals which provide full facilities for early exchange transfusion. In infants very severely affected the clinical condition at birth provides a clear indication for immediate exchange transfusion, and in such cases delay even to complete tests on cord blood is not justified. In less severely affected infants tests of cord blood are required before the need for exchange transfusion can be decided, but in such cases exchange transfusion is not urgently required. When the cord haemoglobin value is less than 11.5 g./100 ml. exchange transfusion is clearly indicated, and we have found it satisfactory to perform this within the first nine hours of life, a time limit arbitrarily laid down for cases included in the British trial of exchange transfusion *versus* simple transfusion in this disease. For infants with higher cord haemoglobin values (80% of all Coombs-positive infants) further tests may be required before the need for exchange transfusion can be decided. The present communication is concerned only with such cases, for in recent years we have been prepared to delay treatment of these up to 16 hours if this proved most convenient.

In order to decide whether this policy is justified we have taken all 80 infants treated between 9 and 24 hours during the past three years and have matched each with a case treated between one and nine hours. Each pair was selected to correspond closely with regard to birth weight and cord haemoglobin and cord bilirubin values. These may not provide perfect controls but they were the best available, and in fact selection for early or late exchange transfusion had depended almost entirely on the time of day at which the infant was born. Thus 80% of those treated late were born between 7 p.m. and 3 a.m. while the reverse was the case for the early group. Individual circumstances had been responsible for the choice of time for exchange transfusion for the 20% of cases not born within these time limits, but there is no evidence that an excess of severely affected infants have been included in the early group because of early jaundice or other evidence of severe disease.

Overall, the onset of jaundice was earlier in the infants whose exchange transfusion was delayed until after nine hours of life. The average bilirubin level at the time of exchange transfusion was 6.95 mg./100 ml. in the cases treated early but 10.44 mg./100 ml. in those treated later. Similarly, there was an increase in the frequency of mild or moderate jaundice, and only five of the late group escaped jaundice whereas 13 of the early cases did so. The frequency of severe jaundice and bilirubinaemia of over 15 mg./100 ml., and the need for repeated exchange transfusion, were the same in both groups. It would appear, therefore, that in moderately affected infants exchange transfusion, even though delayed up to about 16 hours, will prevent the development of severe jaundice, and in the small number of cases where exchange transfusion was delayed beyond the first 16 hours this also seemed to apply. Indeed, 15 of the 19 infants in the late group who developed severe jaundice had been treated in the first 15 hours, and all who required repeated exchange transfusion had been transfused initially within the first 13 hours. There was some suggestion that the older the infant at exchange transfusion the better it tolerated the procedure.

No death attributable to haemolytic disease of the newborn occurred in either group.

If exchange transfusion is delayed too long hyperbilirubinaemia with the attendant danger of kernicterus may occur, and, moreover, exchange transfusion performed initially when the bilirubin has already reached a very high level is less effective in preventing subsequent hyperbilirubinaemia than when performed earlier (Walker, 1959). We think that exchange transfusion should be performed within the first nine hours if an infant is severely affected with haemolytic disease of the newborn. On the other hand, if an infant is not severely affected—that is, the cord haemoglobin value is greater than 11.5 g./100 ml.—exchange transfusion in the first 16 hours of life is usually safe and satisfactory. If the cord bilirubin level is over 5 mg./100 ml., or if early severe jaundice develops, the infant is probably more severely affected than the

cord haemoglobin level suggests and early exchange transfusion is indicated.

There were, in addition to the 80 pairs of cases described, 50 infants with cord haemoglobin values over 11.5 g./100 ml. but who were treated within the first nine hours of life. Evidence has already been presented indicating that exchange transfusion was performed in the first nine hours in some of these either because the cord haemoglobin value was relatively low or because early jaundice developed. In many, however, the time of exchange transfusion and whether or not the case was paired was determined by chance. The subsequent course in these cases did not differ from either of the paired groups. The same proportion developed severe jaundice, a similar number required additional transfusion, and only one infant died, not from haemolytic disease but from hyaline membrane disease. Six of the 50 infants were upset by the transfusion itself, a slightly higher proportion than in either of the other two groups.

Even where haemolytic disease of the newborn has not been predicted, relatively severe disease should be diagnosed within 24 hours of birth, and if prompt exchange transfusion is carried out satisfactory results should be achieved.

Summary

During 1958, 1959, and 1960 we performed exchange transfusion between 9 and 24 hours in 80 infants in whom the cord haemoglobin values exceeded 11.5 g./100 ml. From the same period we selected 80 infants treated between one and nine hours but who were otherwise similar with regard to birth weight and cord haemoglobin and cord bilirubin levels.

Although jaundice was more common in the group treated after nine hours, the frequency of severe jaundice or bilirubinaemia exceeding 15 mg./100 ml. was the same in the two groups, as was the need for subsequent exchange transfusion. There was a suggestion that the infants treated later tolerated the procedure better.

No death attributed to haemolytic disease of the newborn occurred in either group.

We conclude that if the cord haemoglobin value exceeds 11.5 g./100 ml. in the absence of clinical or other evidence of severe haemolytic disease exchange transfusion may safely be delayed up to 16 hours of life.

Acknowledgments are made to the medical and nursing staff of the hospitals concerned, to the staff of the National Blood Transfusion Service, and in particular to Dr. Sheilagh Murray and Dr. George Knox for comments and helpful criticism.

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The London County Council is to resume the recruitment of women ambulance drivers. The service is at present short of 80 drivers—770 are employed but 850 are needed. There is a high rate of wastage and the demands on the service are increasing: 243,342 patients were carried in 1947, 803,134 in 1953, and 1,356,965 in 1960.

CYCLOPHOSPHAMIDE IN TREATMENT OF DISSEMINATED MALIGNANT DISEASE

BY

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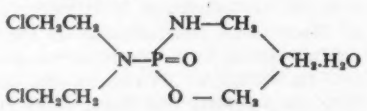
A clinical trial has been undertaken at St. George's Hospital since November, 1959, using a new alkylating agent known as cyclophosphamide ("endoxan," "endoxana," "cytoxan"). This drug was first synthesized in 1958 with the specific purpose of preparing a form of nitrogen mustard which would be inactive when administered and activated only on reaching the site where its therapeutic effect was required. Toxic side-effects should be reduced and tolerance to the drug thereby improved.

Malignant cells are known to be rich in phosphatases and phosphamidases. With this in mind, Arnold and Bourseaux (1958) and Arnold *et al.* (1958) synthesized a number of nitrogen mustard phosphamides and phosphamide esters in the hope that they would be split by these enzymes to an active form within the tumours.

Cyclophosphamide is one of these "transport-form/active-form" compounds. It is a cyclic nitrogen mustard phosphamide ester, belonging to the group of diamide-mono-esters. Arnold *et al.* (1961) consider it to be inert *in vitro* and highly effective *in vivo*. The chemical formula is as follows:



Choice of Cases.—Ninety-two cases with widespread malignant disease have been treated since November, 1959. All these patients were either beyond the scope of conventional forms of therapy or had suffered recurrences after surgery, irradiation, nitrogen mustard, or hormone therapy. Treatment has been undertaken even in the most advanced stages of disease.

Method of Treatment

The recommendations of the German workers (Gross and Lambers, 1958) have been followed in estimating dosage: the amount given has been regulated by the effect of the drug on the haemopoietic system. As a general rule therapy has been started by the intravenous route—with an initial test dose of 100 mg. and subsequent daily doses of 200 mg. intravenously. On occasion this has been increased to 300 mg. and sometimes even 400 mg. daily if there has been no reduction of the circulating white-cell count within five days. This dose has never been exceeded on any one day—except on one occasion, to which reference will be made later.

A deliberate attempt has been made to bring the total white-cell count down to 2,000/c.mm. in order to obtain a maximal anti-tumour effect. It is felt that anything

less drastic is likely to be ineffectual. Less encouraging results reported by other workers may partly be due to inadequate dosage. Intravenous therapy is given until the white-cell level approximates 2,000/c.mm. This usually takes between 7 and 14 days. Oral administration of the drug is then adopted, amounting to 100–200 mg. daily in divided doses to maintain the circulating white-cell count between 2,000 and 3,000/c.mm.; this is continued indefinitely as a maintenance therapy. Some patients may require only 50 mg./day.

Other routes of administration have been used—intrapleural, intraperitoneal, and into the tumour itself—care being taken not to exceed the total dosage of 500 mg. in any one day. Perfusion has not been used in this series.

Initial treatment has nearly always been carried out on in-patients. In the early stages white-cell estimations were made on alternate days. Subsequently, patients who were discharged from hospital on maintenance therapy attended once a week for a routine haematological check, and, if necessary, the dose was adjusted accordingly. On full stabilization this period was extended to one month. Some of the patients in this series have received the drug for more than a year.

The drug is supplied in powder form for intravenous use and is dissolved in sterile water immediately before injection. Oral administration is by tablet.

In order to assess the activity of cyclophosphamide, it has been used alone wherever possible, and not in conjunction with other forms of treatment. Where other therapy overlapped, such cases have not been included in the series: for instance, those patients who were receiving irradiation in conjunction with cyclophosphamide have been excluded, as any improvement may well have been due to the irradiation. The only exceptions to this rule were two patients with carcinoma of the breast who had been receiving hormones (prednisone and testosterone) for some months previously but had relapsed.

Method of Clinical Assessment

The results in any such series are very difficult to judge, particularly if this evaluation is undertaken by many different observers. Moreover, the assessment of subjective improvement is unreliable. The mere fact of admission to hospital often leads to improvement without any treatment.

An attempt was made for all the treated cases to be seen by one or both of two independent observers, and *objective* findings were recorded—such as size of tumour, visible or palpable secondary deposits, and radiological changes in lungs and bones when relevant. Criteria of general well-being, lethargy, pain, nausea, loss of appetite, etc., were noted and any improvement was recorded as *subjective* improvement. The final assessment has been tabulated under these two headings (see Table I).

In an attempt to overcome some difficulties of assessment the method of the mean clinical value introduced by Walpole and Paterson (1949) has been used. Every lesion is allocated a different figure according to whether it remains unchanged, improves, or deteriorates. These marks are estimated at four-weekly intervals, added together, and divided by the number of lesions being assessed. The final figure is then plotted on a graph and the progress of a patient may be seen at a glance (Fig. 1).

Results

Of the 92 patients treated, 16 were excluded for one of the following reasons: (1) drug received for less than two weeks—treatment was regarded as inadequate; (2) documentation was insufficient or follow-up was not possible; and (3) other forms of treatment were used simultaneously.

The remaining 76 cases were assessed (Table I), diagnosis having been confirmed in all instances.

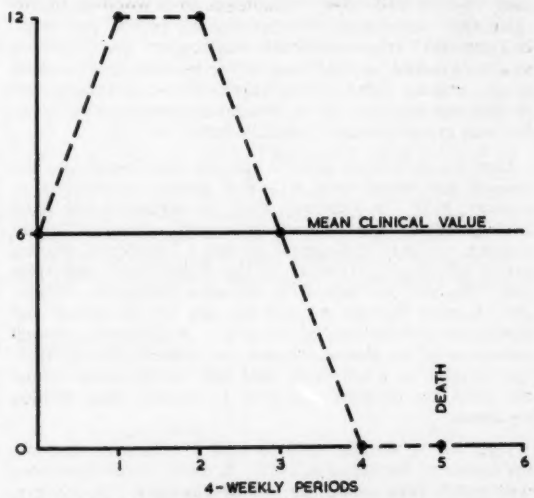


FIG. 1.—Showing initial temporary improvement for an eight-week period and subsequent deterioration and death. This is a typical pattern in those who responded to cyclophosphamide.

TABLE I.—*Objective and Subjective Responses to Cyclophosphamide in 76 Cases. Subjective Response Shown in Parentheses*

Tumour	No. of Cases	No Response	Response for (Months): <3	3–6	6–9	9–12	12+
Carcinoma of breast	20	11	2		1	1 (2)	2 (1)
,, ,, bronchus	27	18	2 (1)	6			
,, ,, pancreas	2	2					
,, ,, ovary	1	1					
,, ,, prostate	1	1					
,, ,, cervix	1	1					
,, ,, rectum	1	1					
Malignant melanoma	1	1					
Hypernephroma	1	1					
Carcinomatosis	1	1					
Sarcoma	3	1	1			1	
Reticulum-cell sarcoma	4	1	1	2			
Lymphosarcoma	4	4					
Hodgkin's disease	5		(1)	1 (1)	1	1	
Mycosis fungoides	1		1				
Myelomonocytic leukaemia	1	1					
Multiple myelomatosis	2			(2)			

It is impracticable to discuss all aspects of individual patients. Diseases which showed some response to treatment have been selected for discussion: (1) carcinoma of the breast, (2) carcinoma of the bronchus, (3) malignant lymphoma, (4) sarcoma, and (5) multiple myelomatosis. These are illustrated by selected case reports.

Carcinoma of Breast

Most of the 20 patients in this group had previously received other forms of treatment—surgery, irradiation, and hormone therapy—but had since relapsed (Table II).

Three very advanced cases were treated with cyclophosphamide as an initial measure: none of these

responded. However, of the 20 patients, six showed objective improvement and a further three subjective improvement.

Case 1.—A woman aged 48 had a mastectomy in February, 1958, followed by deep *x*-ray therapy for carcinoma of the breast. In June, 1959, skeletal metastases appeared. For these she had ovariectomy, prednisone, and subsequent androgen therapy. After an initial response she relapsed and was readmitted in November complaining of malaise and lethargy, and was bedridden owing to severe pain in her back, pelvis, and hips. Radiographs showed extensive ostoeolytic metastases of lumbar spine, pelvis, and skull. In December cyclophosphamide was begun. She responded very well indeed, and returned to her business and was able to go for long walks. Radiographs of the skeletal system showed recalcification of the carcinomatous deposits (Fig. 2). She was symptom-free 18 months later.

Case 3.—A woman aged 50 had pre-operative deep *x*-ray therapy and subsequent left-sided simple mastectomy in January, 1959. In February, 1960, she presented with fixed hard glands in the adjacent axilla and a brawny lymphoedema. A chest radiograph showed a left pleural effusion and a pathological fracture of the fourth, fifth, and sixth ribs. She also had deposits in the spine and pelvis. Cyclophosphamide therapy reduced the size of the glands and diminished the oedema of the arm. Radiographs showed resorption of the pleural effusion and recalcification of bone. She returned to a full day's work and led an active normal life until she relapsed and died 15 months after starting treatment.

Case 4.—A woman aged 58 had a radical mastectomy for cancer of the breast in 1957. In 1959 a local recurrence was treated with prednisone and ovariectomy. In January, 1960, she had multiple skin nodules, one of which was biopsied. A diagnosis of secondary carcinoma was confirmed. She also had severe back pain. Radiographs of the spine revealed osteolytic metastases. Cyclophosphamide

FIG. 2.—Case 1. Radiograph of pelvis (above) before (December 8, 1959) and (below) after (February 10, 1961) treatment with cyclophosphamide. Note recalcification of secondary deposits, especially in right pubic bone.

TABLE II.—*Carcinoma of Breast* (20 *Cases*)

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects: Alopecia	Side-effects: W.B.C. below 1,000/c.mm. at Some Time	Side-effects: Severe Marrow Failure	Clinical Features	Response: Duration	Response: Assessment
1*	48 F	S, X, H	I.V., oral	++	+	–	Continued regression of pulmonary and bone metastases	18+ months	Objective
2	56 F	S, X, H	,,	++	–	–	Regression of metastases in spine and skin, then relapse	12 ,,	,,
3*	50 F	S, X	,,	+	+	–	Improvement of left arm lymphoedema, left pleural effusion, and bone metastases—relapse	11 ,,	,,
4*	58 F	S, H	,,	++	+	–	Disappearance of skin nodules and regression of spine metastases—relapse	8 ,,	
5	56 F	X, H	,,	+	–	–	Regression of left arm lymphoedema, axillary glands, and skin metastases—relapse	2 ,,	,,
6*	61 F	S, X	,,	++	–	–	Recovery from coma and left hemiplegia due to cerebral metastases. Death due to pulmonary embolus	2 ,,	,,
7	59 F	S, X	,,	++	–	–	Recovery from drowsiness, vertigo, nausea, and vomiting due to cerebellar secondary	13+ ,,	Subjective
8	51 F	S, X, H	,,	++	+	–	Breathlessness improved. No change in metastases in glands, bones or lungs—relapse	10 ,,	,,
9	52 F	S, X	,,	++	–	–	Breathlessness improved. No change in pleural effusion—relapse	9 ,,	,,
10	60 F	—	,,	–	–	–	No change in primary lesion or metastases in glands, lungs, or brain	Nil	
11	56 F	S, X	,,	+	–	–	No change in bone metastases	,,	
12	59 F	S, X, H	,,	+	+	–	,, ,, ,, pleural effusion or metastases in glands, chest wall, or skin	,,	
13	51 F	X	,,	–	–	–	No change in primary, glands, or pleural effusion	,,	
14	49 F	S, X, H, thiotepa	,,	+	+	–	,, ,, ,, pleural effusion or lung metastases	,,	
15	56 F	—	,,	+	–	–	,, ,, ,, bone metastases	,,	
16	56 F	—	,,	+	+	+	,, ,, ,, primary. Recovered from marrow failure after temporary cessation of treatment	,,	
17	74 F	S, X	Oral	–	+	–	No change in bone metastases	,,	
18	52 F	X	I.V., oral	–	–	–	,, ,, ,, primary or pleural effusion	,,	
19	54 F	S, X	,,	–	+	–	,, ,, ,, hepatic metastases or ascites	,,	
20	49 F	S, X, H	,,	–	+	–	,, ,, ,, local recurrence, pleural effusion, or bone metastases	,,	

S=Surgery. X=Irradiation. H=Hormonal therapy. * See case reports in text.

was given and an excellent response obtained. The skin nodules regressed completely. Her pain was relieved. She suffered from complete alopecia. She was alive and well nine months after starting treatment.

Case 6.—A woman aged 61 had a left radical mastectomy for cancer of the breast in July, 1959, followed by deep *x*-ray therapy. In November she was readmitted in a semicomatose state with a left hemiplegia which had been developing over the previous two weeks, thought to be due to a cerebral secondary deposit. Cyclophosphamide was given, with a dramatic response. She recovered consciousness and returned to a normal mental state. She regained full use of her paralysed arm and leg, and after six weeks of treatment was able to walk out of the hospital. She died quite suddenly in March, 1960. Necropsy revealed that death was due to a massive pulmonary embolus. The cerebral secondary was confirmed and histological section revealed areas of necrosis.

Carcinoma of Bronchus

Eight of the 27 patients treated showed objective signs of improvement and a further case showed subjective improvement although there was no *x*-ray change (Table III).

Case 21.—In April, 1960, a man aged 65 was admitted to hospital in a moribund state with multiple metastatic skin nodules from a primary bronchogenic carcinoma. Cyclophosphamide produced a dramatic response. The skin lesions disappeared (Fig. 3). His general condition improved and he was discharged five weeks after starting treatment. At four months his condition was unchanged, but five months after starting treatment he was readmitted with a temperature of 102° F. (38.9° C.), signs of bronchopneumonia, and a peripheral white-cell count of 700/c.mm. Cyclophosphamide was stopped. Despite antibiotics he died two days later without evidence of bone-marrow recovery. Necropsy revealed staphylococcal pneumonia and confirmed the presence of an oat-celled carcinoma of the bronchus.

Case 23.—A man aged 40 presented in February, 1960, with superior vena caval obstruction and pain in right chest. Bronchoscopy confirmed carcinoma of the bronchus. Biopsy revealed undifferentiated oat-cell carcinoma. Cyclophosphamide was started. Two months later he had no caval obstruction and no pain. Four months later he was "very well, playing cricket and back at work." But five months after starting treatment there was recurrence of S.V.C. obstruction and he died in September, 1960.

Case 24.—A man aged 55 with carcinoma of the bronchus presented in February, 1960, with shortness of breath,

TABLE III.—*Carcinoma of Bronchus* (27 *Cases*)

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects			Clinical Features	Response	
				Alopecia	W.B.C. below 1,000/c.mm. at Some Time	Severe Marrow Failure		Duration	Assessment
21*	65 M	—	I.V., oral	+	+	+	Regression of pleural effusion and skin metastases. Death due to staphylococcal pneumonia associated with marrow failure. P.M. showed further metastases	5 months	Objective
22	64 M	X	I.V., oral intrapleural	+	+	—	Improvement in pleural effusion and metastases in chest wall. Chest pain diminished—relapse	4 ,,	,,
23*	40 M	—	I.V., oral	+	—	—	Improvement of chest pain, S.V.C. obstruction, gland metastases, and primary lesion (radiograph)—relapse	4 ,,	,,
24*	55 M	—	,,	+	+	—	Regression of oedema left arm and chest wall, pleural effusion, and primary (radiograph)—relapse	3 ,,	,,
25	67 M	—	I.V., oral, intrapleural	—	+	—	Pleural effusion and liver metastases improved—relapse	3 ,,	,,
26	54 M	—	I.V., oral	++	—	—	Headaches due to cerebral metastasis improved. Slight improvement of primary lesion (radiograph)—relapse	3 ,,	,,
27	47 M	S, X	,,	+	—	—	Improvement of S.V.C. obstruction. Chest pain and breathlessness. No change in mediastinal glands—relapse	2 ,,	,,
28	60 M	X	,,	+	+	+	Improvement in fits and paresis due to cerebral metastases and in primary (radiograph). Died after marrow failure with haemorrhage. P.M. revealed progressive metastases	1 month	,,
29	49 F	X	I.V., oral, intrapleural	++	+	—	Improvement of headaches and vomiting due to cerebral metastases	1 ,,	Subjective
30	60 F	—	I.V., oral	++	—	—	No change in cough, pain, gland metastases, or radiographic changes	Nil	
31	46 M	—	,,	—	+	+	No change in pleural effusion or liver metastases. Died with marrow failure and widespread disease	,,	
32	34 F	—	I.V.	—	—	—	No change in primary, lymph node, or haemoptysis	,,	
33	57 M	—	I.V., oral	—	—	—	No change in primary, skin metastases, chest pain, or dyspnoea	,,	
34	49 M	—	I.V.	—	—	—	No change in primary, bone metastases, chest pain, or dyspnoea	,,	
35	62 F	—	I.V., oral	+	—	—	Primary and metastases in glands, liver, and skin all uninfluenced	,,	
36	70 M	—	I.V., oral, intrapleural	—	—	—	No change in pleural effusion or pain	,,	
37	55 M	X	,,	++	—	—	No effect on pleural effusion, pain, breathlessness, or liver metastases	,,	
38	52 M	X	I.V., oral	++	—	—	Primary and glandular metastases unaffected	,,	
39	43 F	—	,,	—	—	—	No change in primary, pleural effusion, or gland metastases	,,	
40	52 F	—	I.V.	—	—	—	Primary and metastases uninfluenced	,,	
41	65 M	—	I.V., oral, intrapleural	—	—	—	Primary, pleural effusion, and glands unchanged	,,	
42	51 M	—	,,	+	—	—	,, ,, ,, ,, ,, ,,	,,	
43	58 M	—	I.V., oral	—	—	—	No benefit upon hemiparesis due to cerebral metastases or primary	,,	
44	54 M	—	,,	+	—	—	Primary and metastases uninfluenced	,,	
45	76 M	—	,,	+	+	—	Primary and metastases in glands and skin all uninfluenced	,,	
46	56 M	—	,,	+	—	—	Primary and widespread metastases unchanged	,,	
47	60 M	—	I.V., oral, intrapleural	+	+	—	,, ,, chest pain uninfluenced	,,	

S=Surgery. X=Irradiation. * See case reports in text.

oedema left arm and left chest wall, severe clubbing, and a liver enlarged four fingerbreadths below the costal margin. Radiograph revealed a shadow in the left upper lobe and a large effusion. Cyclophosphamide started: resolution of the mass on radiograph, complete resorption of the effusion, improvement of general health. He relapsed after three months' treatment and died in July, 1960.

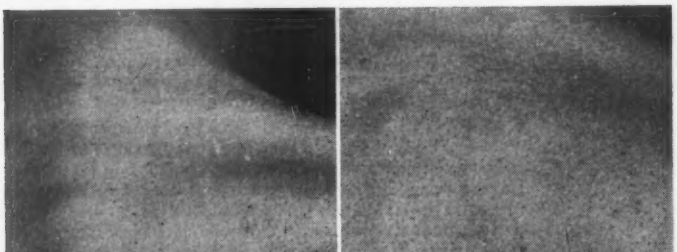


FIG. 3.—Case 21. Metastatic skin nodule from primary carcinoma of bronchus (left) before (April 14, 1960) and (right) after (June 30, 1960) treatment with cyclophosphamide.

Malignant Lymphomas

In this series the following conditions were included under this heading—reticulum-cell sarcoma, lymphosarcoma, Hodgkin's disease, and mycosis fungoides. A total of 14 patients have been treated. Seven showed objective signs of improvement and two others were improved subjectively. Table IV gives details for each subgroup.

Case 49.—A man aged 60 presented in December, 1959, with lymphadenopathy involving cervical, axillary, and inguinal glands. The liver was enlarged four fingerbreadths below the costal margin. Spleen was also palpable. The bone-marrow showed involvement by Hodgkin's disease. He was a very ill man. He had received no other treatment. Cyclophosphamide was given as initial therapy with an excellent response. His general health and appetite improved and his weight increased. All the enlarged glands were reduced in size, showing a marked improvement after only two weeks. He suffered from alopecia. Long-term therapy was continued and he showed no sign of active disease for seven months, but thereafter he relapsed and died nine months after starting treatment.

Case 50.—A man aged 47, a proved case of Hodgkin's disease, was treated in 1958 with mustine (HN2). In January, 1960, he presented with lassitude, apathy, and generalized lymphadenopathy involving glands in the neck, axillae, and both groins. Liver and spleen were enlarged. Cyclophosphamide produced an excellent response, and by the end of four weeks all the glands had disappeared except for two small nodules less than ¼ in. (6 mm.) in diameter. Liver and spleen regressed and were impalpable. Oral therapy was continued, but he suffered a relapse in May, 1960, while still on the drug. Dosage was increased, but he failed to respond and died six months after the beginning of cyclophosphamide therapy.

Case 53.—A man aged 73 presented in March, 1960, with multiple skin lesions involving head, trunk, arms, and legs. He also had a liver enlarged four fingerbreadths below the costal margin. Biopsy showed a reticulum-cell sarcoma. Cyclophosphamide was given with an initial dramatic response. The lesions faded rapidly (Fig. 4). Dosage in this case was higher than usual and increased to 400 mg. a day intravenously. In the third week there was marrow failure, W.B.C. 250/c.mm. Cyclophosphamide was stopped.

TABLE IV.—*Malignant Lymphoma* (14 *Cases*)

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects: Alopecia	Side-effects: W.B.C. below 1,000/c.mm. at Some Time	Side-effects: Severe Marrow Failure	Clinical Features	Response: Duration	Response: Assessment
							Hodgkin's Disease		
48	57 F	X, thiotepa	Oral, intrapleural	+	+	–	Regression of enlarged glands and of pleural effusion. Liver became smaller—relapse	10 months	Objective
49*	60 M	—	I.V., oral	+	–	–	Glands, liver, and spleen all became smaller. General health improved—relapse	6 ,,	,,
50*	47 M	HN2	,,	+	–	–	Improvement in glands, liver, spleen, and general health—relapse	3 ,,	,,
51	40 M	X	Oral	+	–	–	General health improved. Temperature returned to normal and weight increased—relapse	3 ,,	Subjective
52	55 M	X, HN2, T.E.M.	I.V., oral	+	+	–	Improvement of pain due to enlarged glands in pelvis and of pyrexia—relapse	2 ,,	,,
							Reticulum Cell Sarcoma		
53*	73 M	—	Oral	+	+	–	Complete disappearance of multiple skin nodules —relapse	8 ,,	Objective
54	40 M	—	I.V., oral	+	–	–	Regression of glands and improvement of general health	5 ,,	,,
55	35 M	—	I.V.	+	–	–	Complete disappearance of all glands. Death due to meningitis. P.M.—no evidence of lymphoma	1 month	,,
56	64 M	X, S	I.V., oral	–	–	–	No change in oedema of leg or enlarged inguinal glands		Nil
							Mycosis Fungoides		
57	67 F	X, S	Oral	–	+	+	Complete disappearance of skin nodules. Death due to septicaemia associated with marrow failure	2 weeks	Objective
							Lymphosarcoma		
58	46 M	X, CB1348	I.V.	–	–	–	No effect on enlarging glands		Nil
59	62 M	—		–	–	–	Involvement of liver unaffected		,,
60	60 M	X, S, thiotepa	I.V., oral	+	–	–	No change in glands or liver		,,
61	19 M	—	I.V.	–	–	–	Skin metastases unaffected. HN2 also not beneficial		,,

X=Irradiation. S=Steroid therapy. * See case reports in text.

The anaemia and thrombocytopenia were treated with fresh-blood transfusion. Subsequently oral therapy with cyclophosphamide was able to be started. Three months after initial treatment he developed new lesions. He gradually deteriorated and died six months from the time when he was first seen.

Sarcoma

Three patients with sarcoma were treated. Two, suffering from fibrosarcoma of the breast and neurofibrosarcoma of the leg, showed objective improvement.

Case 62.—A girl aged 18 presented in May, 1959, with tumour of the breast which on biopsy was found to be fibrosarcoma (Table V). Mastectomy was performed. Deep *x*-ray therapy was given before the mastectomy. She subsequently developed multiple metastases in the lung fields and a right-sided pleural effusion. Cyclophosphamide was started in October, 1959. There was a gradual regression of all lesions over a period of six weeks as shown by radiography. She developed alopecia. However, she relapsed after this and her condition rapidly deteriorated. A pleural effusion appeared on the left side, although the lesions had almost disappeared on the right (Fig. 5). On two occasions 1 g. of cyclophosphamide was given intrapleurally in addition to her oral dose, but did nof have any effect upon the disease. She developed an intercurrent infection and died with a white-cell count of only 50/c.mm. Reinfusion of the patient's own bone-marrow that had been removed before treatment and stored at −78° C. failed to assist marrow recovery. Necropsy showed extensive disease, but her death was accelerated by marrow aplasia due to excessive dosage. This was the first case treated in this series, and such a large dose has since been avoided.

FIG. 4.—Case 53. Skin lesions in patient with reticulum-cell sarcoma (left) before (February 19, 1960) and (right) after (April 6, 1960) treatment. Subsequently, however, he developed further lesions and gradually deteriorated.

Multiple Myelomatosis

Two patients were treated. Both experienced lessening of bone pain but without improvement of *x*-ray appearances.

Side-effects

Alopecia.—This developed in approximately 60% of cases after three to four weeks of treatment, resulting in complete baldness in approximately one-quarter of all the patients treated. It is a distressing feature, particularly to women. In the majority of patients who survived there was a new growth of hair while on maintenance therapy, but it was often stunted and a wig was necessary. All patients who were given this drug were warned of this consequence before starting treatment.

Bone-marrow Failure.—A deliberate attempt was made to reduce the total white-cell count to approximately 2,000/c.mm. as an indication of effective dosage. In some cases, however, it fell even further. As any patient whose white-count fell to 1,000/c.mm. or less was thought to be subject to danger, the routine adopted was to stop the drug, give wide-spectrum antibiotics, and, if necessary, a fresh-blood transfusion. Experience has shown that if the patient survives, the white-cell count will recover spontaneously within four to seven days of stopping the drug. This difference between cyclophosphamide and other drugs closely related is not yet explained (Pegg, 1960), but is an undoubted advantage of cyclophosphamide. Altogether there were 28 cases (37%) whose white-cell count fell below 1,000/c.mm. In all but five recovery of bone-marrow function occurred, but in these five death occurred with marrow aplasia and an overwhelming infection. In four of these patients the lesions were not responding to the drug and they would have succumbed to their disease within a very short time; the remaining patient, however, died two weeks after starting treatment while her lesions were undergoing a marked regression. In most patients there was some fall of haemoglobin level

TABLE V.—*Sarcoma* (3 *Cases*)

Case No.	Age and Sex	Previous Treatment	Cyclophosphamide Treatment. Routes of Administration	Side-effects: Alopecia	Side-effects: W.B.C. below 1,000/c.mm. at Some Time	Side-effects: Severe Marrow Failure	Clinical Features	Response: Duration	Response: Assessment
				Fibrosarcoma of Breast					
62*	18 F	S, X	I.V., oral, intrapleural	+	+	+	Regression of pulmonary metastases and recurrence in chest wall. Death associated with marrow failure and widespread disease	2 months	Objective
				Neurofibrosarcoma					
63	52 F	S	I.V., oral	+	−	−	Regression of pulmonary metastases	9+ ..	..
				Spindle-cell Sarcoma of Chest Wall					
64	44 M	X	..	+	−	−	No change in lesion of chest wall		Nil

S = Surgery. X = Irradiation. * See case report in text.

while on intravenous therapy, but only eight patients (11%) required blood transfusion. Macrocytosis was always evident during treatment. Platelets were rarely depressed to below 100,000/c.mm. and only one case required fresh-blood transfusion, for melaena and haematuria due to thrombocytopenia. The white cells have been a most sensitive index of toxicity. The detailed haematological effects of this and other cytotoxic agents will be the subject of a separate communication.

Nausea and Vomiting.—This has occurred in approximately one-quarter of all patients, but in only one case was it severe enough to cause treatment to be abandoned: it was controlled with anti-emetics and sedatives.

Survival Time

Long-term results are not encouraging (Table I). Despite initial improvement most cases relapsed while on treatment. Only seven patients showed objective improvement for a period longer than six months; a further three were classified as obtaining subjective improvement over the same period.

Discussion

Cyclophosphamide seems to be of value in the management of advanced malignant disease. Of the 76 patients treated in this series, 23 showed a definite objective and measurable improvement and a further eight subjective improvement. The range of malignant conditions benefited by this drug is very similar to that reported by other workers using related compounds of the nitrogen mustard group. The encouraging short-term results reported here may be due in part to the relatively high dosages of the drug given, as judged by the degree of leucopenia produced.

Varying degrees of success have been reported by other workers using cyclophosphamide in a wide range of malignant disease (Gross and Lambers, 1958; Snyman and Falkson, 1960; Korst *et al.*, 1960; Matthias *et al.*, 1960; Molin, 1961; Stoll and Matar, 1961).

Cyclophosphamide has certain advantages over many of the currently available cytotoxic drugs. Unlike mustine (HN2) injection presents no specific problems, for it is stable in aqueous solution and has no vesicant effect on tissue. Oral administration is effective and so allows maintenance therapy. It is felt that continued treatment has produced longer remissions than those reported by Stoll and Matar (1961) using single massive doses in advanced breast cancer.

The final method of action of cyclophosphamide is similar to other alkylating agents. Actively dividing cells in all tissues, particularly in the tumour and in the bone-marrow, are subject to damage. Radioactive studies by Bolt *et al.* (1961), using tritium-labelled cyclophosphamide, have shown that the highest concentration of the drug is in the primary tumour and its metastases.

A certain degree of peripheral leucopenia is expected and is used as an indication of adequate treatment. If excessive damage to the bone-marrow occurs, with depression of the circulating white cells and platelets, immediate withdrawal of the drug is nearly always followed by recovery of bone-marrow function within four to seven days, when treatment may be resumed. Such prompt haematological recovery is not seen after the use of other related drugs and allows patients to receive more effective dosages without the danger of marrow failure lasting many days. However, particular care should be taken when giving cyclophosphamide to patients who, prior to treatment, are known to have bone-marrow depression due to malignant infiltration of the marrow or to previous irradiation therapy.

Alopecia is a most distressing side-effect for the patient, and occurs more often than with other nitrogen mustards. It is our practice to warn all patients of this

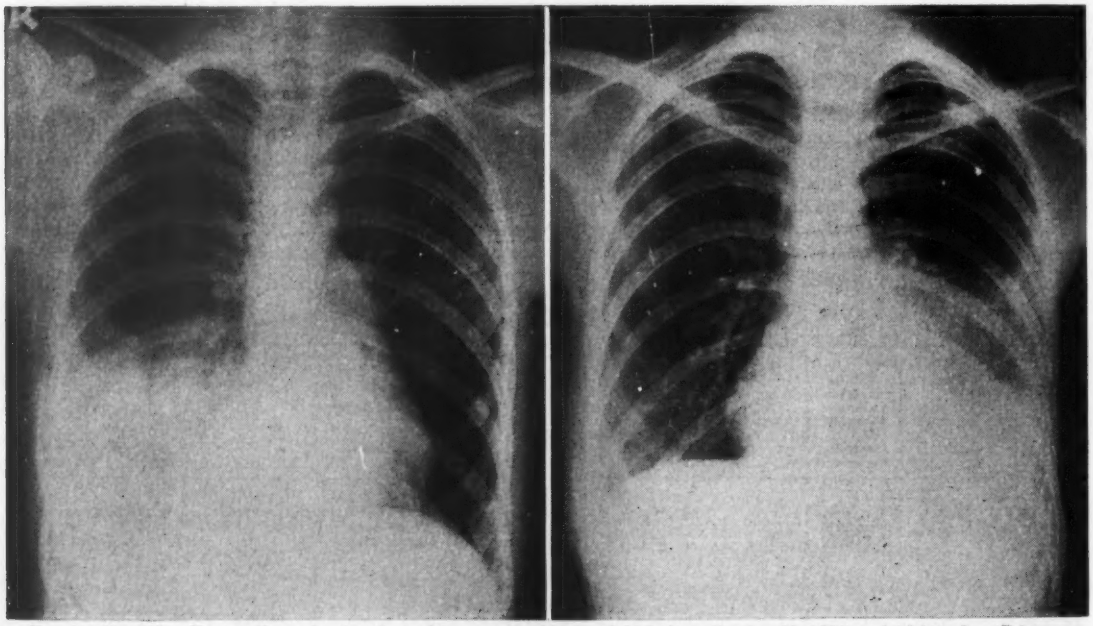


FIG. 5.—Case 62. Chest radiograph of patient with sarcoma of breast (left) before (October 29, 1959) and (right) after (February 4, 1960) treatment. Note pulmonary secondary deposit and effusion on right side have completely resolved—although new lesion has developed on the opposite side.

possibility in advance, but it was never felt to contra-indicate treatment, as the hair regrows during maintenance therapy.

Nausea and vomiting may occur, but this depends on the dosage and susceptibility of the patient. The severity and incidence of this side-effect is, in our opinion, less than that seen using comparable doses of mustine (HN2) or thiotepa.

Cyclophosphamide has been used by other workers as a prophylactic measure in conjunction with surgery. Denk *et al.* (1961) report a series of 282 cases of carcinoma of the bronchus which have been treated chemotherapeutically for two years after radical operation, and claim that at 18 months the survival rate was 81% compared with 42% without the drug. This form of treatment has not been used in this series.

The long-term results are not encouraging in the present series despite continued treatment. Only two patients, both with carcinoma of the breast, responded for more than one year and only one of these remained symptom-free after 18 months.

Summary

A series of 76 cases of disseminated malignant disease have been treated with cyclophosphamide (a cyclic nitrogen mustard phosphamide ester). Twenty-three of these cases showed an objective response. Long-term results are not encouraging. Complications and side-effects are discussed. It is suggested that treatment with cyclophosphamide is worth while in patients with advanced malignant disease, although response is often short-lived.

We are grateful to Mr. Victor Riddell, who was the first person to draw our attention to the potentialities of cyclophosphamide. We are indebted to Dr. J. L. Stafford for much helpful advice, and to other members of the consultant staff of St. George's Hospital who have allowed their patients to be included in this series. We thank the photographic department of St. George's Hospital for the illustrations, and Dr. J. M. Simister, of Ward, Blenkinsop & Co. Ltd., for supplies of the drug. One of us (N. H. K.) acknowledges his gratitude to the British Empire Cancer Campaign for a full research grant during the tenure of which much of this work was carried out.

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"Science is rarely advanced by what is known in current jargon as a 'break-through.' Rather does our increasing knowledge depend on the activity of thousands of our colleagues throughout the world who add small points to what will eventually become a splendid picture, much in the way that the Pointillistes built up their extremely beautiful canvases." (Anniversary address to the Royal Society by Sir HOWARD FLOREY, P.R.S.)

HIGH-DOSE NITROGEN MUSTARD THERAPY WITH INTERMITTENT AORTIC OCCLUSION

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Nitrogen mustard (methyl-*bis* (β-chloroethyl) amine, HN2) is an alkylating agent widely used in the treatment of malignant disease (Rhoads, 1946). Alkylating agents are believed to interfere with tissue growth by reacting with the cellular nucleic acids (Zamenhof *et al.*, 1956; Stacey *et al.*, 1958). This effect is not tumour-specific, and the highest degree of inhibition appears to be achieved with tissues undergoing the most rapid replacement. Apart from tumour tissue, these include bone-marrow, lymph nodes, and intestinal epithelium.

HN2 produces cellular damage in these tissues which can readily be observed histologically as early as one day after administration (Sternberg *et al.*, 1958). Biological evidence of its cytocidal effect *in vivo* can be obtained as early as 10 minutes after administration (Burchenal *et al.*, 1951). The kinetics of the affected cell type determine the timing of the clinical symptoms. Lymphocyte depression may become apparent within hours, intestinal disturbances—rarely at conventional doses—within days. Three weeks may elapse before the depression of the white-cell precursors is fully reflected as leucopenia in the peripheral blood. For all practical purposes, the effects of several doses of HN2 given within a short period of time appear to be cumulative for the proliferating tissues.

In addition, there are effects of HN2 which are not related to cell reproduction but concern the nervous system and produce symptoms immediately. While nausea and vomiting are often observed with conventional doses, fatal convulsions, like those occurring in cats after high doses (Sternberg *et al.*, 1958), have not been observed in man after systemic administration of tolerated mustard doses. There is no conclusive evidence that effects on the nervous system are cumulative if HN2 is administered in fractionated doses.

Clinically, the most important manifestation of mustard toxicity after systemic administration is bone-marrow depression. The dose which can be tolerated by the patient is the dose from which his bone-marrow can recover before fatal complications occur. Therefore attempts have been made to raise the concentration of

HN2 in the tumour tissue without increasing the amount of drug affecting all or parts of the bone-marrow. They can be classified as follows: (1) Local administration into malignant effusions (Karnofsky *et al.*, 1948). (2) Administration into the artery supplying the tumour area (Klopp *et al.*, 1950; Cook, 1959). (3) Regional perfusion by temporary exclusion of the tumour-bearing area from the general circulation (Creech *et al.*, 1958). (4) Systemic administration with protection of parts of the bone-marrow by (*a*) removal and storage of bone-marrow before drug administration (Clifford *et al.*, 1961), or (*b*) temporary occlusion of the abdominal aorta and collateral arteries during and shortly after drug administration (Miller and Lawrence, 1961). Essential for the procedures outlined under Nos. 3 and 4*b* is the fact that HN2 is active in the circulating blood for less than 10 minutes (Ryan *et al.*, 1958).

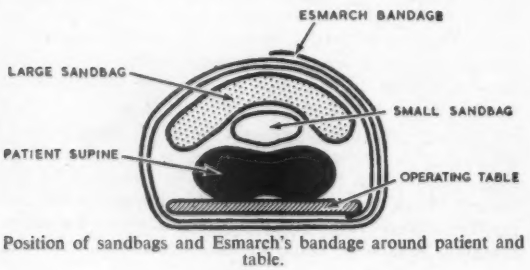
The lack of radiotherapy in Kenya and the high incidence of head and neck cancer (Clifford, 1960) have led to the use of HN2 in increasingly high doses. The impression was formed that the degree and duration of the anti-tumour effect was related to the quantity of the drug administered. With protection by autologous marrow, as a free graft (Clifford *et al.*, 1961), HN2 has been given in this department in doses of 2 mg./kg. with safety.

For cancer localized above the diaphragm, temporary occlusion of the abdominal aorta appeared to represent a possibility to protect parts of the haematopoietic tissue while obtaining a high concentration of the drug in the tumour area by intravenous administration. The observations of Miller and Lawrence (1961), that a single dose of 1.2 mg. of HN2 per kg. administered by this method produces eighth-nerve damage, suggested that effects on the nervous system limit the amount of drug which can be given as a single dose without serious complications. Since it was possible to give 2 mg. of HN2 per kg., divided into five doses, to patients protected by bone-marrow grafts (Clifford *et al.*, 1961) without producing symptoms attributable to damage to the central nervous system, it was thought that fractionation of the total dose might also be usefully combined with aortic occlusion.

The objective was to develop a technique which would make practicable repeated aortic occlusions within a period of a few days. This method is referred to as intermittent aortic occlusion (I.A.O.).

Technique

The patient, under full relaxant anaesthesia, is placed supine on a firm-topped operating-table. A small sandbag, 6 by 6 in. (15 by 15 cm.), is placed in the space bounded by the rib cage and the iliac crests, and a large sandbag 9 by 18 in. (23 by 45 cm.) is laid across this. An Esmarch bandage binds the bags firmly into the abdomen by passing tightly around sandbags, patient, and table (see Diagram). The aorta is thus compressed against the lumbar spine, and most collateral vessels are also occluded. Cessation of the femoral arterial pulse indicates a satisfactory occlusion. The occlusion is maintained for 20 minutes, and is repeated during the next 48 hours. The total dose of HN2 is calculated on an mg./kg. body-weight basis. HN2 in a concentration of 1 mg./ml. of 0.9% saline is freshly prepared. On cessation of the femoral pulse, one-quarter of the total dose is injected into an arm vein over a period of two minutes. After 10 minutes the second quarter dose is given. After a further 10 minutes the tourniquet is released and the patient returned to the ward. The second half of the dose is given within 48 hours in a similar manner.



Position of sandbags and Esmarch's bandage around patient and table.

The plasma volume was determined using Evans blue, T-1824, and a method based on that of Mollison *et al.* (1950). The total blood volume was calculated from the plasma volume and the venous haematocrit. These studies indicated that aortic occlusion reduced the circulating blood volume to approximately one-half. Evans blue was injected into the cephalic vein immediately after occlusion. After an interval of 15 minutes, while the aorta was still occluded, blood was removed from the femoral vein. No dye could be demonstrated, indicating the effectiveness of the occlusion.

Intravenous pyelograms, taken during an aortic occlusion, demonstrated normal excretion of the dye through both kidneys. Thus, despite the width of the occluding bags, the occlusion appears to be effective distal to the renal arteries.

Sternal and iliac bone-marrow aspirations were performed in eight cases under anaesthesia prior to the first occlusion. Leucocyte and platelet counts were also taken at this time and at regular intervals thereafter on all patients. Sternal and iliac bone-marrow aspirations were performed 10 days after occlusion and sternal marrow aspirations six weeks after occlusion in eight and six patients respectively.

Results

Ten patients with advanced neoplastic disease have been treated with I.A.O., using doses from 1.5 to 3 mg. of HN2 per kg. (Table I).

TABLE I.—*Summary of Clinical Details*

Case No.	Histological Diagnosis	Previous Treatment*	Total Dose HN2 (mg./kg.)	Estimated Effective Tumour Dose (mg./kg.)	Therapeutic Response
1	Anaplastic carcinoma post-nasal space	1	2·0	3·7	+++
2	" "	2	1·86	3·4	+
3	" "	1	1·5	2·75	++
4	" "	2+3	1·6	2·9	++
5	Undifferentiated carcinoma oesophagus	4	1·6	2·9	Died
6	Anaplastic carcinoma post-nasal space	4	1·8	3·3	+
7	" "	4	2·5	4·5	+
8	" "	4	2·5	4·5	+
9	Carcinoma oesophagus	4	3·0	5·5	+++
10	Anaplastic carcinoma post-nasal space	4	1·5	2·75	+

* 1=Continuous interarterial infusion of methotrexate and intermittent intramuscular injection of "leucovorin." 2=Methotrexate, chlorambucil, and actinomycin D combined, single daily doses. 3=HN2 1 mg./kg., two courses. 4=No previous treatment.

+=Moderate decrease in tumour size. ++=Marked partial regression of tumour. +++=Complete tumour regression and negative biopsy from previous site of tumour.

Case 1

An African man aged about 30 was admitted to hospital on November 1, 1960, complaining of a swelling in the left neck, pain in the left ear, and sore throat with dysphagia of two months' duration. On examination there was a mobile swelling 3 by 2 in. (7.5 by 5 cm.) overlying the left sternomastoid muscle. A friable, readily bleeding tumour 1 by ¼ in. (25 by 0.6 cm.) was visible in the nasopharynx on the left side. Biopsy of this showed an anaplastic carcinoma.

Treatment. — Metabolite/antimetabolite chemotherapy (leucovorin and methotrexate) failed to produce tumour regression, and by January 2, 1961, the soft palate was displaced forward by the tumour. On January 10 and 12, HN2 2 mg./kg. was given with occlusion.

Post-operative Course.—Severe vomiting and diarrhoea persisted until January 18, necessitating intravenous fluids. Marked improvement in the intraoral picture was noted on January 18, and by February 21 there was no visible tumour in the post-nasal space (P.N.S.). The large left neck tumour had disappeared, leaving some small hard discrete neck glands. On March 15 a biopsy from a P.N.S. curettage showed "the only evidence of neoplasia to be a minute collection of cells with bizarre nuclei and mitoses in a corner of the specimen."

A repeat biopsy on March 30 showed no evidence of malignancy in the specimen. April 2: Marked shedding of the scalp hair; no palpable neck glands. May 1: No intraoral growth or neck glands apparent. On May 5 the patient was discharged symptomless and apparently free from disease.

Case 2

An African boy about 16 years of age was admitted to hospital on September 22, 1960, complaining of deafness, persistent headache, nasal obstruction, pain on the right side of the face, and blindness in the right eye. On examination the boy was ill and wasted, with massive bilateral cervical adenitis and a neck circumference of 20 in. (51 cm.). A persistent purulent nasal discharge with complete obstruction to both nares was noted. There was no apparent growth in the P.N.S., although the mucosa appeared hypertrophic. Marked proptosis of the right eye, a sixth-nerve paresis, and blindness of the same eye were present. *X*-ray examination showed considerable destruction of the right posterior ethmoidal cell system. Biopsy of a neck gland showed anaplastic carcinoma.

Treatment.—A course of oral methotrexate, chlorambucil, and actinomycin D combined in conventional dosage failed to have any therapeutic effect. On January 17 and 19, 1961, HN2 1.86 mg./kg. was given with occlusion.

Post-operative Course.—After three days of severe vomiting and mild diarrhoea the patient noted a decrease in his facial pain, and the neck masses felt less tense. January 26: Neck circumference was 18 in. (46 cm.) and there was no facial pain. February 20: After being symptom-free for three weeks he had a recurrence of the pain. There had been no further decrease in the size of the glands. February 24: The general condition began to deteriorate, and it was not thought justifiable to attempt further occlusive therapy. February 28: After a steady worsening in the general condition and intractable pain the patient died. Post-mortem examination was not permitted.

Case 3

An African girl aged 15 was admitted to hospital complaining of severe bleeding from the left nostril, toothache, and earache on the left side and a swelling in the left neck. On examination a hard fixed swelling involving the entire left half of the soft and hard palates was present. A friable bleeding growth filled the left nostril. There was a hard fixed gland, 2 by 1 in. (5 by 2.5 cm.), at the angle of the left mandible and small shotty glands were palpable in the right neck. *X*-ray examination showed destruction of the posterior wall and floor of the left maxillary antrum. Biopsy from the nose revealed a markedly undifferentiated squamous-cell carcinoma.

Treatment. — Metabolite/antimetabolite chemotherapy via the left external carotid artery failed to produce satisfactory tumour regression, and the severe epistaxis was causing concern. On January 17 and 19, 1961, HN2 1.5 mg./kg. was given with an occlusion.

Post-operative Course.—A mild post-operative vomiting passed off in 48 hours. The drug otherwise was well tolerated. Diminution in the size of intraoral growth and the neck glands was noted at the end of the first week. March 3: Progressive improvement in the general condition occurred, and there was no further epistaxis. The left nostril was clear of growth and patent. A swelling in the palate, although smaller than before occlusion, was still present. March 18: Biopsy from the post-nasal space showed persistence of malignant cells. March 27 and 29: HN2 2.75 mg./kg. was given with occlusion, and there were no untoward effects. Progress was maintained until April 24, when the patient became jaundiced. Liver-function tests suggested a hepatocellular cause presumed due to the high dosage of HN2. This complication resolved on treatment with prednisone, vitamin K, and dietary restriction. Progress was then uneventful, except that moderate alopecia appeared on May 8. At this date no intraoral growth could be demonstrated. On May 30 a left Caldwell–Luc operation was performed for persistent opacity of the left maxillary antrum. At operation the posterior bony wall of the antrum was absent, and the cavity contained pus. There was no macroscopic evidence of malignancy in the P.N.S. Specimens from the P.N.S. and antral lining showed no microscopical evidence of malignancy.

Convalescence was uneventful and the patient was discharged on June 19, symptom-free.

Case 4

An African child aged 10 years was admitted to hospital on August 22, 1960, complaining of a swelling in the left side of the neck of three months' duration. On examination there was a large tumour overlying the left sternomastoid muscle, oval in shape and firmly fixed to underlying structures. The neck circumference was 16 in. (40.5 cm.). There was no evidence of disease in the nose or throat, and no other lymph nodes were palpable. Biopsy from the neck showed an anaplastic carcinoma but post-nasal curettage revealed normal adenoid tissue only.

Treatment.—HN2 was given without occlusion, using 1 mg./kg. as a total dose given over five days. One week after completion of the course the neck measurement was 14 in. (35.5 cm.). Two weeks later the measurement was 13 in. (33 cm.). Tumour was still present, but as the white-cell count was normal the course of HN2 was repeated. Two weeks after this second course the neck measured 15 in. (38 cm.) and 10 days later it was 17 in. (43 cm.). With the obvious advancement of the disease it was decided to give methotrexate, chlorambucil, and actinomycin D in conventional dosage. This therapy produced a 1-in. (2.5-cm.) decrease, which was sustained for one week only. At this juncture the patient caught chicken-pox. On January 25 and 27, 1961, HN2 1.6 mg./kg. was given, with occlusion. This was followed by mild vomiting and bloody diarrhoea. Culture of the stool revealed *Shigella flexneri*, which resolved on chloramphenicol. After this recovery was uneventful. The circumference was 18 in. (45.5 cm.) on January 27, 16 in. (40.5 cm.) on February 14, 14 in. (35.5 cm.) on February 25, and 16 in. (40.5 cm.) on March 10.

Although the general condition was still good on March 16, the disease was obviously progressing. It was decided that nothing further could usefully be done, and the patient was repatriated and was lost to follow-up.*

*This unfortunately occasionally happens, owing to the remoteness of some parts of the country and absence of communications.

Case 5

An elderly African man was admitted to hospital complaining of complete dysphagia. On examination a feeble, grossly cachectic, bedridden old man was seen. Oesophagoscopy revealed a large ulcerous mass obstructing his cervical oesophagus. Biopsy showed an undifferentiated carcinoma.

Treatment.—HN2 1.6 mg./kg. was given with occlusion. The patient succumbed on the fourth post-occlusal day. Post-mortem examination was not permitted.

Case 6

An African man aged about 50 was admitted to hospital on January 9, 1961, complaining of right-sided pain and headache of four months' duration with loss of vision in the right eye. On examination diffuse enlargement of the right face was present, with complete right ophthalmoplegia, and paralysis of the fifth, seventh, eighth, and twelfth cranial nerves on the same side. There were enlarged fixed glands on both sides of the neck. Rhinoscopy and biopsy confirmed the diagnosis of an infiltrating anaplastic carcinoma of the nasopharynx.

Treatment.—On January 29 and 31 HN2 1.8 mg./kg. was given with occlusion.

Post-operative Course.—The treatment was well tolerated apart from transient vomiting on February 6. Blistering was apparent, overlying the course of the superficial veins (in all cases they turned black and thrombosed). By February 12 the facial pain had decreased, and by February 23 the neck glands were smaller, discrete, and mobile. The pain had disappeared. Despite no change in the neurological status, he was still free from pain on March 20, and with the suggestion of further biopsy he discharged himself and did not return.

Case 7

An African woman aged about 45 was admitted to hospital on January 19, 1961, complaining of dysphagia, purulent nasal discharge, and trismus. On examination there were multiple shotty nodes on both sides of the neck and paresis of the third, fourth, sixth, and seventh cranial nerves on the right side. The right ear was partially deaf. Intraoral examination was impossible owing to trismus. Biopsy of the nasopharynx revealed an anaplastic carcinoma.

Treatment.—On February 5 and 7 HN2 2.5 mg./kg. was given with occlusion.

Post-operative Course.—Deterioration in her general condition from vomiting and mental confusion caused some concern, but these symptoms passed off after seven days. February 15: No nasal discharge, but superficial ulcers were apparent on the lips and nasal mucosa. February 21: No neck glands palpable; general condition good. She continued to gain weight, but there was no change in the neurology. The ulcers had healed with local toilet. April 14: Nasopharyngeal biopsy showed no evidence of malignancy. April 26: Repeat biopsy again negative. April 29: Audiogram showed a hearing loss of 50–70 decibels to all frequencies on the right and of 50 decibels to all frequencies above 1,000 c.p.s. on the left. May 5: Discharged asymptomatic, but with neurological status unchanged. May 10: Seen as an out-patient. General condition very good. Mentally bright. Still partially deaf but has adequate social hearing. No macroscopic evidence of disease.

Case 8

An African man aged about 50 was admitted to hospital on January 20, 1961, complaining of headache and left-sided neck swelling. Examination on January 30 showed a thin wasted man with a fixed round swelling in the left neck. Rhinoscopy revealed a hard nodular swelling in the nasopharynx, and biopsy of this and the neck swelling showed an anaplastic carcinoma.

Treatment.—On February 14 and 17 HN2 2.5 mg./kg. was given with occlusion. This was not well tolerated, and the post-occlusal week was marked by severe vomiting and mild diarrhoea. On February 18 he had a generalized fit lasting about three minutes. Mental confusion was marked for about two weeks after this. On February 28 the neck glands were reduced in size, but biopsy of the glands was still positive on March 30, when they were about half the size at admission. A course of 2.5 mg. of HN2 per kg. was given on May 5 and 7. This course was not well tolerated. Severe mental confusion was noted, and vomiting and diarrhoea were severe. There was marked regression of the neck glands, which were impalpable by the end of the second week.

The patient's general condition, however, continued to deteriorate, and by May 27 he had become completely apathetic, incontinent of urine and faeces, and unwilling to take food. His condition remained the same until June 18, when he started getting generalized convulsions. On June 26 a lumbar puncture revealed a C.S.F. pressure of 300 mm. fluid and normal chemistry. Progression of the growth into the brain was suggested or cerebral metastasis. His general condition deteriorated until July 14, when he caught chicken-pox. He became progressively weaker and died on July 25.

Post-mortem Examination.—Almost complete destruction of the basisphenoid was seen. The sphenoidal sinus and pituitary fossa were filled with a mass of necrotic material which involved the infundibulum and hypothalamus. No healthy residual tumour tissue was noted.

Case 9

An African man of about 35 was admitted to hospital on February 2, 1961, with a six-months history of dysphagia, and ability to swallow only fluids. Barium-meal examination revealed a stenosis of the mid-oesophagus with rat tailing, and oesophagoscopy confirmed an ulcer at 23 cm., histologically due to an anaplastic carcinoma. No secondaries were found.

On February 13 and 15 3 mg. of HN2 per kg. was given with occlusion. There was no significant vomiting, but the patient complained of tinnitus. After one week he was swallowing semi-solids with little difficulty. A barium-meal examination on March 10 showed a near-normal oesophagus with a marked improvement of flow compared with the pretreatment pictures. On March 17 the dysphagia returned, he was unable to take semi-solids, and fluids regurgitated. Oesophagoscopy showed no ulceration, but there was a tight constriction at 23 cm., which was dilated. A biopsy taken at this time showed sheets of fibrous tissue containing nests of malignant cells.

On April 5 and 7 further treatment with HN2 3 mg./kg. was less well tolerated than the first course. Vomiting and diarrhoea were severe and dizziness, headache, and marked tinnitus were complained of. There was severe mental confusion for two weeks. On April 11 dysphagia became complete again and a Ryle tube was passed. Oesophagoscopy on April 19 revealed a tight stricture at 23 cm. and an intact mucosa. Biopsy showed no evidence of malignancy on serial section. A Jaques tube was inserted, being left in place until May 2. A barium swallow on May 2 showed a stricture 1 in. (2.5 cm.) above the aortic arch. The patient still complained of tinnitus and loss of balance. Audiograms showed a severe loss beyond 1,000 c.p.s. Swallowing was still difficult, necessitating tube-feeding. Oesophagoscopy on May 31 showed a non-ulcerating stricture. This was dilated and a biopsy taken. There was no evidence of malignancy in serial sections. Swallowing improved after this until June 24, when dilatation was again performed. Biopsy was again negative. On June 28 the patient complained of hoarseness and pain in the throat, and an oedematous paralysed left cord was seen, thought to be due to involvement of the left recurrent laryngeal nerve by fibrosis. Oesophagoscopy and dilatation were carried out on July 11. Biopsy was negative. The left cord was still oedematous and paralysed. At this juncture it was decided

to bypass the stricture by bringing up a loop of colon. This was performed on July 31. Despite an apparently favourable operative course, the patient died the same night.

Post-mortem Examination.—No obvious cause of death was apparent at necropsy. The oesophageal primary appeared as a tight ball of fibrous tissue. Ulceration was not present. The laryngeal symptoms were due to an abscess containing a small bone, which had penetrated the oesophagus and localized itself just below the vocal cords. Microscopy of the specimen revealed a dense stroma of fibrous tissue in which were embedded nests of malignant cells. The change from frank anaplasia to this fibrotic appearance is interesting.

Case 10

An elderly African man was admitted to hospital on January 16, 1961, complaining of pain and swelling of the left side of the face for six months. On examination he was wasted, dehydrated, and very weak. The left side of the face was diffusely swollen, with a marked seventh nerve palsy. The third, fourth, sixth, and twelfth cranial nerves were paralysed on the left. There was a large hard fixed swelling 3 by 2 in. (7.5 by 5 cm.) overlying the right sternomastoid muscle. Marked trismus precluded adequate intraoral examination. Rhinoscopy and biopsy under anaesthesia confirmed the diagnosis of an infiltrating anaplastic carcinoma of the nasopharynx.

Treatment.—On February 27 and March 1 HN2 1.5 mg./kg. was given with occlusion.

Post-operative Course.—Apart from mild transient vomiting and mental confusion, the drug was well tolerated. On March 5 the tumour was noticeably smaller and on March 10 it measured ½ by ½ in. (1.3 by 0.6 cm.) and was mobile. On March 30 a small tumour was still palpable in the neck. Despite all measures the patient remained thin and weak. It was thought not justifiable to subject him to further treatment and he was repatriated. The neurological status remained the same.

TABLE II.—*Results of Haematological Studies*

Case No.	Before I.A.O.		After I.A.O.					
	Bone-marrow		10 Days		6 Weeks	Days to Lowest W.B.C.	Lowest W.B.C.	Days to Normal W.B.C.
			Bone-marrow					
	Sternal	Iliac	Sternal	Iliac	Sternal Bone-marrow			
1	3	3	1	4	2	22	4,050	24
2	3	3	0	4	N.T.	11	2,100	15
3	3	3	0	4	3	11	1,000	22
4	3	3	1	4	N.T.	No data		
5	No data							
6	3	3	0	4	3	10	1,600	17
7	3	3	1	4	3	10	2,600	15
8	3	3	1	4	2	7	350	14
9	3	3	0	4	3	11	850	14
10	N.T.	N.T.	N.T.	N.T.	N.T.	No depression		

0=Aplastic. 1=Very hypoplastic. 2=Hypoplastic. 3=Normoplastic. 4=Hyperplastic. N.T.=Not taken.

TABLE III.—*Toxic Effects Observed in* 10 *Patients*

Case No.	Immediate				Delayed		
	Vomiting	Diarrhoea	Mental Confusion	8th-nerve Impairment	Life-threatening Complications Due to Leucopenia	Gastro-intestinal Disturbance	Alopecia
1	3	3	0	1	0	0	1
2	3	1	0	0	0	0	0
3	2	0	0	1	0	0	0
4	1	Shigella	0	0	0	0	0
5	No data						
6	1	0	0	0	0	0	2
7	2	0	2	1	0	0	1
8	3	1	2	0	0	0	3
9	0	0	0	1	0	0	4
10	1	0	1	0	0	0	0

Estimated effective tumour dose as in Table I. 0=Absent. 1=Mild. 2=Moderate. 3=Severe. 4=Very severe.

The haematological response in each of the cases is outlined in Table II.

Discussion

Ten patients with inoperable neoplastic disease were treated with HN2 administered intravenously in doses far higher than are normally regarded as safe. It has been demonstrated in nine cases that the technique described provides adequate protection of the pelvic bone-marrow against up to 3 mg of HN2 per kg.

Only two patients (Cases 3 and 9) have admitted to having symptoms referable to the eighth nerve after doses of 1.5 and 3 mg./kg. Audiometric studies in four cases revealed a marked loss of auditory function in the range above 1,000 cycles per second, suggesting eighth-nerve damage. The nature of these effects is being investigated further.

McFarland *et al.* (1959) noted at necropsy severe maceration of the gastro-intestinal mucosa after 1.4 mg. of HN2 per kg. Despite doses ranging from 1.5 to 3 mg./kg. fulminating gastro-intestinal toxicity has not been noted. Anorexia, nausea, and vomiting, common side-effects even after conventional doses of HN2, were observed in all patients during the first days after drug administration.

Alopecia was noted only when doses of 1.8 mg./kg. or more were administered. Three patients appeared mentally confused. So far as can be judged at the present time, alopecia and confusion would appear to be reversible. These factors are being further investigated.

One patient (Case 5) was admitted in poor general condition due to long-standing malignant stricture of the upper oesophagus. He died on the fourth day after I.A.O. Permission for necropsy was not obtained. There was no clinical or laboratory evidence that his death was related to treatment with HN2. Cases 1, 3, 4, and 9 showed remarkable tumour regression. This and the fact that no positive biopsy could be obtained in two cases after treatment can be fully evaluated only after a longer follow-up period. The fact that Case 4 had not responded previously to two courses each of 1 mg./kg., yet had good partial tumour regression after 1.6 mg./kg. with aortic occlusion, would appear to deserve attention.

The effect of further fractionation of the total dose of HN2 on frequency and severity of toxic symptoms, particularly those related to the central nervous system, is under investigation at the present time.

Summary

A simple technique of intermittent occlusion of the abdominal aorta and of collateral arteries is described.

The occlusion is effective enough to allow the administration of up to 3 mg. of HN2 per kg. divided into four doses without fatal bone-marrow injury, as shown in 10 cases of inoperable cancer localized above the diaphragm.

Toxic effects have been vomiting, diarrhoea, alopecia, mental confusion, and decrease of auditory function.

Preliminary evidence of tumour regression justifies further studies with this method of treatment.

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CAROTID PAIN: REPORT OF SIX CASES

BY

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As a presenting symptom, severe spontaneous pain felt over the bifurcation of the common carotid artery has been reported by few medical writers. Fay (1927, 1932) described that physical sign which he termed "carotidynia," tenderness along the course of the common carotid which may be elicited during an attack of atypical facial neuralgia. He used this in support of his hypothesis that in such cases headache was brought about by abnormal behaviour of the carotid tree.

The first description of spontaneous carotid pain as a symptom appears to have been made by Truffert (1948). He recorded, in a man of 38, episodes of severe pain at the level of the carotid bifurcation, sometimes radiating upwards into the face. He described a feature which is very characteristic of the syndrome, the extreme sensitiveness of the artery to the slightest pressure, so that the wearing of a light scarf would cause an intolerable aggravation of the pain. He also noticed, during attacks, the appearance of a pulsating tumour at the level of the hyoid. In the same paper two other cases were also described. In 1949 Hilger published an account of five cases similar to those of Truffert, and Riser, Dardenne, and Gleises (1949) described the case of a 78-year-old man whose carotid pain evidently fell into a clinical category distinct from the previous cases and indeed from all subsequently published cases. In this case, although bilateral carotid pain was a presenting symptom, a diagnosis of temporal arteritis was made, and was supported by biopsy.

A case of recurrent carotid pain associated with angioneurotic oedema was reported by Martorell (1955). The most recent and the largest series is that of Lovshin (1960), who analysed the case histories of 100 patients seen in two years at one clinic. Though only three detailed histories are used in illustration, he drew a vivid composite picture of the syndrome which he regarded as "a vascular headache in the neck," and he made a plea for its wider recognition. I have been unable to find any British references to this striking and singular clinical phenomenon.

The six cases described below were first seen during the period April, 1959, to June, 1961.

Case Reports

Case 1.—A married woman of 47 was sent by her G.P. to an ear, nose, and throat surgeon, complaining of a very painful swollen "gland" in the left side of her neck. This had troubled her intermittently for seven months in about 10 episodes of between one and seven days' duration. The pain would sometimes spread up the left side of the face to the temporal and parietal region. For 12 years she had been subject to migraine, paroxysms of fronto-parietal headache lasting 48 hours, which she regarded as entirely distinct from her pains in the neck. She was a tense, anxious woman obviously in great pain. A pulsatile tumour was seen and felt on the left side at the level of the carotid bifurcation. The lightest palpation of it caused great distress. Elsewhere the vascular system appeared normal and the patient was normotensive. A slow intravenous injection of ergotamine tartrate, 0.5 mg., failed to relieve her pain or to lessen the tumour. She has been reviewed at intervals over the two-year period and has had a number of similar attacks. During this time there have been many other complaints for which no organic basis could be found. They included soreness of the eyes, low back pain, and pain on micturition. She suffered also from neurodermatitis. She gave, and continued to give, the impression of a sad, rather lonely woman in need of sympathy.

Case 2.—A married woman of 58 complained of soreness in an "inflamed gland" in the neck on the left. She had a long history of ill-health, including three nervous breakdowns of many months' duration. These appeared to have been exacerbations of a long-standing and almost continuous phobic anxiety state. She had within the previous year complained of abdominal pains which had defied diagnosis, and she had been treated by manipulation, and, unsuccessfully, for low back pain. She was a sad-looking woman with a fear of cancer. The left common carotid was readily palpable and was very tender at the level of bifurcation. There was no glandular enlargement in the neck. Her blood-pressure was 160/90.

Case 3.—A machine-tool fitter aged 51 complained of pain below the right angle of the jaw in episodes of two hours at exactly the same time every afternoon for the previous five days. He had had "a nervous breakdown" at the age of 16 and a tendency to occasional headache of short duration all his life. A well-built man of healthy appearance, he gave his story simply and without embroidery. The right common carotid was very tender at its bifurcation and pulsated more amply on this side. The fauces were healthy and there was no lymph-node enlargement. The blood-pressure was 195/100. The pain was unrelieved by intravenous ergotamine tartrate. The E.S.R. was 26 mm. in one hour. A week later there was still a complaint of occasional dull pain but tenderness was no longer apparent. Within a further week all pain had gone and the E.S.R. had fallen to 6 mm. in the hour. During the next two years he experienced occasional attacks of neck pain but was never again observed in one of these.

Case 4.—A male laboratory technician aged 40 noticed tenderness in the right side of the neck. Whenever he touched a certain point he experienced pain which shot up into the ear and side of his face. Shaving over the affected area had become intolerable for this reason, and sneezing, coughing, or slight movement of the head caused an intense pain in the neck. Five days before the onset he had contracted a sore throat and head cold. He had always regarded himself as a healthy person, although until a year before this he had suffered occasional attacks of migraine which he recognized as quite different from the pain in his neck. Examination revealed no signs of ill-health apart from extreme tenderness of the right carotid bifurcation. There was no evidence of pharyngeal inflammation nor of any gland enlargement. Within two weeks of its onset the pain cleared up and had not returned during the next 18 months.

Case 5.—A 34-year-old male medical practitioner noticed what he took to be a "sore throat" affecting the right side only. On the following day, swallowing or even yawning was very painful and the pressure of a shaving-brush was unpleasant. At this time there was some vague backache which lasted 24 hours. On the third day the pain had diminished but the common carotid artery was very tender. By the fifth day all pain and tenderness had gone. There has been no recurrence in two years.

Case 6.—A woman of 69 experienced pain in the right side of the throat, aggravated by swallowing and by turning her head to the left. She was, by personal experience, acquainted with the symptoms of acute pharyngitis: this, she said, felt quite different. During the previous week she had had a slight head cold which had cleared up before the onset of the pain. The pain had been sudden in onset, reaching maximum intensity within a few minutes. She was a person who usually enjoyed excellent health. The throat was healthy and no glands were felt. The right carotid bifurcation was very tender. Within 48 hours she was free from pain. There has been no return of pain in two months.

Discussion

Clinical Picture.—The feature common to all these case histories is a complaint of pain in one or other side of the neck and of great tenderness, usually to the lightest touch, over the corresponding carotid bifurcation. In one patient, during an attack, the carotid artery at this point was visibly swollen, and in two others the amplitude of pulsation was tangibly greater on the affected side. In Cases 1 and 3 the neck pain has been recurrent, while in Cases 4, 5, and 6 the symptom appears to have been an isolated phenomenon: the short follow-up period does not permit any such conclusion in Case 2. In two of the cases in which pain occurred as a solitary episode the onset was preceded by a head cold.

Aetiology.—"We do not know whether the pain is due to simple arterial dilatation or whether there is another factor such as sensitization of the pain nerve-endings by a chemical agent." These words, written by Sir George Pickering in 1939, referred to the cause of migrainous headache, but they are equally applicable to-day to the cause of carotid pain, and the similarity of the two problems is evident. Lovshin (1960) suggested that carotid pain and tenderness were brought about by arterial dilatation and that "vascular" neck pain is no more than a variant of "vascular" headache. This contention is supported by the spread of pain, when severe, to the face and scalp, as in Cases 1 and 4 of the present series. Case 4, where the pain occurred with clockwork precision at the same time every afternoon, is reminiscent of Bickerstaff's (1959) description of the periodic migrainous neuralgia of Wilfred Harris. Although in two patients an intravenous injection of ergotamine tartrate failed to modify the pain, it has been shown by Torda and Wolff (1945) that prolonged dilatation of an artery will result in oedema and stiffening of the vessel wall, rendering it no longer susceptible to vasoconstricting drugs. It is, however, doubtful if any good purpose is served at the present time by the comparison of one syndrome which is barely recognized with a group of others which are barely understood, although it is worth stressing that in none of the migraine-type headaches is there that extreme arterial tenderness which is found with carotid pain and which is comparable only to the tenderness of temporal arteritis.

Prevalence.—The carotid-pain syndrome is not the rare condition implied by its scant acknowledgment in the literature of medicine. Three patients were seen at one medical clinic in little more than two years, while three others were brought to my notice by an interested colleague during the same period. The apparent rarity of the syndrome is probably due to our failure to recognize it. We cannot recognize something of which we are not already aware, and it is hoped that this paper may, by creating awareness, stimulate the recognition and study of a very singular phenomenon in vascular behaviour.

Summary

Reports are given of six patients in whom pain in the neck was accompanied by great tenderness of the common carotid artery. It is thought that this may be a common syndrome, at present seldom recognized.

My thanks are due to Dr. Glyn Walters for his continued interest and help with this study.

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The *President's Review* from the *Rockefeller Foundation Annual Report, 1960,* shows that out of the Foundation's grants of $32,833,971 in 1960 nearly a third ($10,250,060) went to the medical and natural sciences. The Foundation's total income for the year was nearly $24m. and the market value of its uncommitted principal fund at the end of the year was nearly $470m. During 1960 234 new Fellows from 39 countries and three international organizations began advanced study, and 345 Fellows continued their work; Fellows studied at 159 institutions in 22 countries. In his review President J. G. HARRAR points out that the Foundation is placing increased emphasis on training individuals from many countries for leadership in national and international developments. A survey is given of the support the Foundation lends to work on the arthropod-borne diseases of man and his domestic animals.

THRUSH IN THE NEWBORN

BY

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Candida albicans is often found as a saprophyte in the adult mouth, yet whenever these yeast-like fungi are isolated from the mouth of the newborn baby clinical thrush is either present or will become apparent in four or five days (Anderson *et al.*, 1944 ; Harris *et al.*, 1958 ; Kozinn *et al.*, 1958).

The variations in the reported incidence of oral thrush (Table I) may depend on the following factors: (1) Adequacy of treatment of monilial vulvovaginitis in the mother (see below). (2) Early discharge of babies from hospital, very few cases being detected before the seventh day (see below). (3) Thoroughness of daily examination of the baby's mouth.

TABLE I.—*Reported Incidence of Oral Thrush in the Newborn*

Author or Institution	Year	Newborn in Series	Oral Thrush	
			No.	%
Epstein	1924	2,500	150	6·0
Ludlam and Henderson (1942)	1942	{ 60 2,540	11 163	18·3 6·4
Anderson *et al.* (1944) ..	1944	107	20	18·8
Maimonides Hospital ..	1955	3,600	36	1·0
	1956	2,175	69	3·1
Beth El Hospital	1955	3,500	5	0·14
Mount Sinai Hospital ..	1955	4,000	20	0·5
Queen Charlotte's Hospital	1955–9	14,873	95	0·66

Reproduced in part from Kozinn *et al.* (1958).

Clinical Thrush in the Newborn

In the milder cases a few white patches appear on the buccal mucous membrane or tongue which, unlike milk curds, cannot be removed by gentle swabbing. In the more severe case the entire lining of the mouth appears as if heavily frosted and the infant becomes irritable, refusing feeds and losing weight. If the lesion extends to the pharynx and oesophagus, an event fortunately uncommon (Ebbs, 1938 ; Lederer and Todd, 1949 ; Dobias, 1955 ; Drouhet, 1955 ; Wolff *et al.*, 1955), an apparent incoordination of the swallowing mechanism occurs, with regurgitation of blood-stained vomitus, aspiration pneumonia, and usually death.

Serious septicaemia may occur with involvement of kidneys and meninges (Ludlam and Henderson, 1942 ; Lederer and Todd, 1949 ; Wolff *et al.*, 1955). Most of these infants have received prolonged antibiotic therapy. Wolff *et al.* (1955) record recoveries after the use of intravenous hydroxystilbamidine, while Drouhet (1958) successfully used oral nystatin in doses up to 2 million units a day for an infant.

The fungus may pass through the bowel with or without diarrhoea, to appear as perianal thrush. Taschdjian and Kozinn (1957) found *C. albicans* invariably in the stools of those who carried the organism in the mouth ; of these, 50% developed clinical perianal thrush. Ammoniacal dermatitis, which affects mainly the convexities of the buttocks, must be distinguished from thrush, which usually starts at the perianal margin, spreading outwards with an irregular wet-blotting-paper-like fringe with peripheral satellite patches.

Bodian (1958) describes four necropsies on newborn infants where thrush was found and was thought to be an index of debility associated with a malformation or prematurity, but not a cause of death. Lederer and Todd (1949) thought that fatal thrush might be undetected on account of diagnostic difficulties both in life and after death. Oral thrush, although not usually serious, is not innocuous and may lead to an overwhelming infection. Ten deaths due to thrush during the newborn period were registered in England from 1952 to 1957 (Corkindale, 1960). Untreated oral thrush may resolve in about 30 days (Kozinn *et al.*, 1958) ; treated in about 30 hours. The presence of oral thrush is a potential threat to the infant, and all cases should be treated when diagnosed.

Present Study

This study correlates the presence of thrush in the newborn with monilial vulvovaginitis in the mother. Various factors claimed to predispose to thrush were also investigated.

All the women attending the antenatal department during the five-year period 1955–9 who complained of soreness and pruritus with or without obvious discharge, and who were found to be harbouring *C. albicans* in the vagina, were included in this series. Each day the infant's mouth was examined for suspicious patches, and all those from whom *C. albicans* was isolated form the newborn section of this series.

During this period there were 14,873 live births, of whom 1,106 (7.3%) were premature. Monilial vulvovaginitis was found in 232 of the mothers at some time during their pregnancy (Table II)—that is, an incidence of 1.5% of live births. Oral thrush developed in 95 babies. The correlation of maternal vulvovaginitis, treated or untreated, with the incidence of thrush in their offspring, is recorded in Table III.

TABLE II.—*Time when Monilial Vulvovaginitis Diagnosed*

Week	0–12	13–20	21–28	29–36	37–40
Percentage ..	2	13	24	43	18

TABLE III.—*Correlation of Maternal Monilial Vulvovaginitis with Oral Thrush in the Newborn*

Antenatal Status of Mother			Newborns with Thrush	
Monilial Vulvovaginitis	Treatment	No. of Cases	No. of Cases	Percentage
Absent	Nil	14,641	75	0·5
Present ..	Adequate	210	5	2
,, ...	Inadequate*	13	8	60
,, ...	Nil	9	7	77

* Inadequate treatment implies the persistence of the illness before the birth of the baby and/or the detection of *C. albicans* during the puerperium.

Treatment of Monilial Vulvovaginitis

Nystatin vaginal tablets (100,000 units) inserted twice daily for at least two weeks will cure most cases. Occasionally a patient may require even more prolonged treatment. Decreasing the duration of therapy leads to an increase in failures and relapses (Abbas, 1958 ; Donald, 1958 ; Jennison, 1958) and a probable increase in the number of infants who will develop oral thrush.

Table IV records the varied treatments used in this series. In some cases more than one preparation was needed.

Table V notes the details of treatment given to 13 mothers whose infants developed thrush. In Cases 1–8

the treatment was inadequate, and the discharge either persisted or *C. albicans* was found in the vagina during the puerperium. These cases were not treated for long enough, or may have relapsed. Cases 10–12 were treated adequately, but a bacteriological relapse may have occurred later in pregnancy.

TABLE IV.—*Treatments for Monilial Vulvovaginitis Used in this Series*

Preparation	No. of Cases	Percentage
Nystatin	69	30
Gentian violet	50	22
'Aci-jel'	34	15
Glycerin and borax	34	15
Hydrargaphen	15	7
Diiodohydroxyquinolone	10	4·5
Chlorphenesin	9	3·5
S.V.C.	4	2
Mercurochrome	2	1
	227	100%

TABLE V.—*Details of Treatment Given to Mothers with Vaginal Moniliasis whose Babies Developed Thrush*

Case No.	Week of Diagnosis	Treatment	Days	Discharge Present at Onset of Labour	Postpartum *C. albicans*	Breast or Bottle	Day of Onset in Baby
1	26	Gent. violet. Nystatin	7 7	Yes	Yes	Breast	3
2	22	Gent. violet	7	,,	,,	,,	5
3	36	Mercurochrome	2	,,	,,	,,	6
4	8	Gent. violet	7	No	,,	,,	8
5	38	Hydrargaphen	5	Yes	No	Bottle	9
6	13	Aci-jel. Gent. violet. Hydrargaphen. Gly. and borax	10 10 14 14	,,	Yes	,,	10
7	39	Gent. violet	3	,,	,,	Breast	6
8	30	,, ,,	7	,,	,,	,,	7
9	21	Di-iodohydroxyquinoline	7	No	No	Bottle	15 (prem.)
10	31	Nystatin	14	,,	,,	,,	4
11	18	Gent. violet	14	,,	,,	,,	7
12	34	,, ,,	14	,,	,,	Breast	8
13	38	Nystatin ,,	4	,,	,,	,,	10

At every antenatal visit direct questioning regarding the presence of vulval itching and discharge should alert the practitioner to the possibility of moniliasis. After mycological confirmation, adequate therapy should be advised. If the illness was first detected early in pregnancy, and adequately treated, a relapse may still occur, and this should be looked for at about the 36th week.

Untreated monilial vulvovaginitis appears to be associated with a higher incidence of thrush in the newborn than when adequately treated. The lowest incidence is found in mothers who have no clinical evidence of infection. In this series (Table III) 14,641 pregnant women with no antepartum history of vaginal moniliasis produced 75 infants who developed thrush, an incidence of 0.5%. Yet nine women with untreated vaginal moniliasis produced seven infants who developed oral thrush—an incidence of 77%. The 210 women with moniliasis "adequately" treated produced but five infants with oral thrush—that is, 2%—and this figure might have been further reduced by more prolonged or repeated treatment later in pregnancy in some of these patients. Thirteen infants developed thrush when the mothers had been treated for monilial vulvovaginitis, and in 8 (60%) the treatment was obviously inadequate—in another 3 probably inadequate.

Bret and Coupé (1958) could not isolate the organism from any newborn when the organism was not found in the mother's vagina during pregnancy. Harris *et al.* (1958), investigating 1,442 pregnant women, found *C. albicans* in 254 during early labour. In this group 20% of their infants harboured *C. albicans* in the mouth and over half developed clinical thrush. In the group where the organism could not be found, only 1% of their infants developed thrush.

Dawkins *et al.* (1958) found *C. albicans* in the vagina in 7% of non-pregnant women, 20% of pregnant women, and only 3% during the puerperium. This apparently spontaneous cure after delivery may explain those cases where thrush is found in the newborn although the organism cannot be isolated from the mother after the birth of the baby.

Newborn thrush is found more often when the mother harbours the organism during early labour (Harris *et al.*, 1958) or even more so when frank monilial vulvovaginitis is present (Kozinn *et al.*, 1958).

Although Dawkins *et al.* (1958) found *C. albicans* in 20% of their pregnant patients, at the 16th or 28th or 32nd week, in only 8.3% was there a positive culture on all three occasions. In only one case was oral thrush found in the baby—in this mother *C. albicans* was found on all three occasions. Thus the later *C. albicans* is found during pregnancy the more likely is it to influence the incidence of oral thrush in the newborn.

These yeast-like fungi are seldom isolated from the atmosphere, and all infections appear to have an endogenous source (Conant *et al.*, 1954; Van Breusegham, 1958).

The present concept that most infants are inoculated in transit through the contaminated vagina is confirmed by this series. But the vagina is not the only source (see Table VI).

Browne (1950) states that in maternity hospital nurseries thrush is endemic and every outbreak should be investigated, as the infection is readily conveyed by nurses' hands, utensils, milk, and other means. Bound (1958), discussing perianal moniliasis which often developed after the baby had been taken home, could find oral thrush in but one-third of his cases and suggested that the infection may have been transferred by the mother's contaminated hands when changing napkins.

TABLE VI.—*Possible Source of Infection*

Source	Author
Vagina	Dobias (1955). Harris *et al.* (1958). Kozinn *et al.* (1958).
Nipple	Nelson (1959)
Infected bottles and utensils	Browne (1950). Ferguson and Rothman (1956). Nelson (1959)
Poor nursery hygiene	,, ,, ,, ,,
Contact with infected infants	,, ,, ,, ,,
Contaminated hands of mother or nurse	Brown (1950). Bound (1958)
Infected sputum in mother	Present author

TABLE VII.—*Thrush in Infants Born by Caesarean Section*

Case No.	Vulvovaginitis	Membranes Ruptured	*C. albicans* Postpartum	Breast or Bottle	Source of Infection
1	No	No	Negative	Breast	Not found in mother's mouth, nipple or vagina
2	,,	30 min.	,,	,,	Mother a chronic bronchitic—on antibiotics throughout pregnancy. *C. albicans* in sputum
3	,,	No	,,	,,	Not found. Mother had monilial dermatitis two years before
4	Yes. Emergency admission. Gent. violet paint to vagina for 3 days	19 hours	Positive	Bottle	? Ascending infection. ? Contamination of mother's hands
5	Yes. Emergency admission	19 ,,	,,	,,	,, ,,

Most recent authors favour the vaginal source of infection and regard hospital contamination as being responsible for relatively few cases of thrush (Bret and Coupé, 1958; Harris *et al.*, 1958; Kozinn *et al.*, 1958).

In one large series—that of Kozinn—no infant born by caesarean section developed thrush, and this enhanced the idea that all cases of thrush in the newborn developed after passage through the infected vagina. In this series, however, there are five cases of newborn thrush in which delivery was by caesarean section. Details are given in Table VII.

Predisposing Causes

It is not quite clear why *C. albicans* is usually pathogenic in the mouth of the newborn. Normally multiplication of these organisms is held in check by the natural defence mechanisms of the body, and various authors have suggested that the following *host-factors may increase the newborn's susceptibility to oral thrush* (Winner, 1958): (1) prematurity; (2) debility; (3) diabetes; (4) antibiotic therapy; (5) steroid therapy; (6) local trauma to the baby's mouth during aspiration or resuscitation; and (7) *p*H of the newborn's mouth.

Prematurity.—Harris *et al.* (1958) found that 20% of his group of 34 infants with oral thrush were premature, whereas the incidence of prematurity in the entire group was only 5%. Kozinn *et al.* (1958) could find no more cases among the prematures than among the full-term. Eighty-seven of our cases weighed over 5 lb. 8 oz. (2,500 g.), leaving eight as prematures—that is, oral thrush developed in 0.64% of mature babies and 0.7% of premature babies. Prematurity *per se* does not seem to be a predisposing factor. Boys and girls were equally affected, and no seasonal incidence could be found for the onset of thrush in either mother or baby.

Antibiotics.—During this period approximately 700 infants were given antibiotics—only four of these developed thrush. Antibiotics did not appear to predispose the newborn to thrush during the first 10 days as only 4 of the 95 who developed thrush had received any antibiotics. Neither breast- nor bottle-feeding favoured the development of oral thrush in the newborn (see Table VIII).

TABLE VIII.—*Effect of Feeding on Incidence of Thrush in Newborn*

Type of Feeding	Babies with Thrush	Unaffected Babies
Breast	64%	70%
Bottle	22%	20%
Mixed	14%	10%

TABLE IX.—*Age when Thrush Detected in the Newborn*

Day	0–3	4–6	7–10	11–14	Over 14
No. of cases ..	2	10	72	9	2

Faulty hygiene and contaminated milk do not seem important as a source of infection in this series.

Thrush was usually detected at the end of the first week, most cases becoming apparent by the seventh day (see Table IX).

pH of Mouth of the Newborn.—The increased incidence of monilial vulvovaginitis is attributed in part to increased acidity of the vagina during pregnancy (Donald, 1958). The *p*H of the mouth of 30 infants was tested throughout the first 10 days of life and the majority revealed a *p*H of 7–8. One case developed thrush, but the *p*H was unaltered. Neither breast- nor bottle-feeding had any obvious effect on the *p*H.

Trauma.—It was difficult to assess the influence of trauma to the oral mucosa on the development of thrush. If anything, the babies with thrush had required less resuscitation than the unaffected infants; thus trauma *per se* does not seem to be an important factor.

Treatment of Oral Thrush in the Newborn

Almost all cases have responded to either topical gentian violet (aq. solution 0.5) or nystatin suspension (100,000 units per ml.) four or five times a day until the mouth was clear, plus an extra two days to prevent a relapse (Table X).

TABLE X.—*Treatment Used in Oral Thrush of Newborn*

Gentian violet (aq. solution) 0·5% as drops	53 cases
Nystatin suspension (100,000 units/ml.) ..	39 ,,
Both above	3 ,,

Gentian violet is a cheap satisfactory treatment in most cases, and is best dispensed in a dropper-bottle with instructions to apply three or four drops under the tongue after feeds. The baby's moving tongue will then paint the mouth. This is more effective, quicker, and less messy than trying to paint the patches with a cotton-wool swab soaked in gentian violet solution. In two cases thrush did not respond to gentian violet but disappeared when nystatin was used. In one case there was no improvement with nystatin but rapid response to gentian violet. Probably gentian violet should be tried first, keeping nystatin for resistant cases. This may also prevent the emergence of nystatin-resistant strains.

Complications

During this period of investigation two cases of perianal thrush were detected in the neonatal period and one case of diarrhoea which responded to oral gentian violet.

Discussion

Prematurity, method of feeding, *p*H of the baby's mouth, trauma, or antibiotics during the neonatal period do not appear to predispose the baby to oral thrush. Untreated vaginal moniliasis will produce a high incidence of affected infants, whereas adequately treated mothers have a very much lower incidence of thrush in their offspring. It would appear that thrush in the newborn could be prevented in most cases by controlling maternal vaginal moniliasis. Should the mother require to be treated early in pregnancy, a possible relapse should be looked for later. Because *C. albicans* is so often found as a commensal in the vagina and the post-partum cure rate is so high, it is doubtful whether routine search for *C. albicans* and subsequent treatment of the "positive" cases is justifiable. Dawkins *et al.* (1958) found only one case of thrush in their series of 250 women.

Although the vagina is the most likely source of infection, there are others, and an infant born by caesarean section may develop thrush. The organism may pass from the mother's mouth or hands to the baby, but these routes are uncommon and can be avoided by routine post-partum hygiene.

Whether the baby gets thrush from the nipple or vice versa is difficult to decide, although one case of nipple thrush was eradicated by treating the baby's mouth.

Daily inspection of the infant's mouth by the mother or nurse, with mycological confirmation of suspicious patches and immediate treatment, will probably control all cases. The daily routine swabbing of infant's mouth for *C. albicans*, and treating when found, or the routine use of prophylactic nystatin has proved successful (Harris *et al.*, 1958 ; Larroche, 1957, quoted by Drouhet, 1958), but it is doubtful whether such measures are necessary. No great harm will ensue if the lesion is missed for a day or two. The microscope and medication should complement and not replace the clinician. (Again, we may produce a resistant strain by these techniques.)

Summary

The incidence of thrush in the offspring of mothers with untreated monilial vulvovaginitis is very high, decreasing towards zero as the treatment becomes more adequate. Prematurity, breast- or bottle-feeding, antibiotics, or *p*H of the baby's mouth are *not* predisposing factors. The vaginal route of infection appears to be the most common. Early clinical detection of infected mothers and infants, and treatment with gentian violet or nystatin will control the disease.

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SCLEREMA NEONATORUM TREATED WITH CORTICOSTEROIDS

BY

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Before 1948 the survival rate for sclerema neonatorum was about 25% (Hughes and Hammond, 1948). Infants who recovered were full-term with birth weights of over 5½ lb. (2,500 g.). Since then case reports have appeared of patients treated with A.C.T.H. and corticosteroids. We have been able to trace 17 infants in the English medical literature who have received these hormones for the treatment of sclerema neonatorum, and 16 of them survived—some of them being premature. The greatest number of cases in any given series was four (Kendig and Toone, 1951 ; Kendall and Ledis, 1952 ; Glynn Williams, 1953 ; Kurzrok, Marshall, and Becker, 1954 ; Eisenoff, Aaron, and Green, 1954 ; McDonald, 1955 ; Buess, 1955 ; Davis, 1955 ; Wickes, 1956). So far as we are aware no statistically valid series has been published in which the value of corticosteroids in the treatment of sclerema neonatorum has been assessed.

We are fortunately placed for assessing the value of corticosteroids in this condition, because cold injury in the newborn infant is of common occurrence in the African population served by this hospital. This is particularly so in premature infants, of whom 635 were admitted during 1959, most of them less than 4½ lb. (2,040 g.) in weight. In this paper we compare the results of treatment of sclerema neonatorum with and without corticosteroids.

Material and Methods

During a nine-month period in 1959 we were able to collect 25 neonates with sclerema neonatorum who were admitted to the lying-in wards, the premature-baby unit, or the paediatric wards of Baragwanath Hospital. The diagnosis was made by at least two of us, and we were guided by Hughes and Hammond's (1948) definition of this condition—namely, that it is "characterized by a diffuse rapidly spreading, non-oedematous, tallow-like hardening of the subcutaneous tissue of infants in the first weeks of life. The skin in involved areas cannot be picked up and the subcutaneous tissues seem bound down to subjacent muscle and bone." All children in this series had non-pitting induration of the skin and subcutaneous tissues in several of the following sites: cheeks, deltoid and scapular regions, arms, forearms, buttocks, and lower limbs. The sclerema was widespread in all but five cases—that is, three or more sites were extensively involved. Of the five infants with less extensive sclerema, two had involvement of the cheeks alone, one showed sclerema of the lower limbs, one of the cheeks and legs, and one of the forearms, legs, and scapular region.

The general therapeutic measures carried out on all the babies in this series were as follows: (1) warming by means of an electric pad, blankets, and cotton-wool

wrap; (2) administration of oxygen through a funnel at the rate of 2 litres a minute for cyanotic attacks; (3) omission of feeds where the rectal temperature was below 95°F. (35°C.), and (4) intravenous-fluid therapy via a scalp vein in the presence of dehydration.

It was our plan to treat alternate cases with and without steroids. Owing to staff changes this plan was not always adhered to, some cases being treated by our colleagues according to their own preference. As these cases occurred at random, they did not,* we think, introduce a bias into the treatment groups.

There were 11 patients in the series receiving corticosteroids (group A), and 10 of them were given 50 mg. of hydrocortisone sodium succinate by intramuscular injection when the diagnosis of sclerema was made. This was followed by 25 mg. intramuscularly every 8–12 hours for up to five days. One child in this group received A.C.T.H. by intramuscular injection in doses of 10 units every six hours, while another received 10 units daily for three days after completion of a course of hydrocortisone. Penicillin was administered to 9 of the 11 infants in doses of 50,000–100,000 units every eight hours by intramuscular injection. In four of them 50 mg. of streptomycin sulphate was given every 12 hours by intramuscular injection, and in two cases chloramphenicol was given additionally in doses of 30–50 mg./lb. (66–110 mg./kg.) body weight per 24 hours.*

The 14 infants in group B did not receive corticosteroids. Five were not given antibiotics, and penicillin was administered to the remaining nine by intramuscular injection in the doses mentioned previously. Four infants received streptomycin in addition, while two others were given chloramphenicol by mouth.*

Results

Table I summarizes the body weights, clinical features, extent of sclerema, and post-mortem findings (where available) of the 11 infants in group A.

*Chloramphenicol was administered in these relatively high doses before reports appeared of its toxicity in neonates (Kent and Wideman, 1959; Sutherland, 1959; Burns, Hodgman, and Cass, 1959).

All were premature infants whose birth weights ranged from 2 lb. 6½ oz. to 4 lb. 15½ oz. (1,090 to 2,250 g.), six of the infants weighing 3 lb. (1,360 g.) or less. The total dose of hydrocortisone administered ranged from 50 to 275 mg., while a total dose of 60 units of A.C.T.H. was given to the single patient treated with this hormone alone.

The most frequent associated illnesses noted in this group were diarrhoea, usually with dehydration, and clinical "bronchopneumonia." All patients with adventitious sounds in the lungs were regarded as cases of "pneumonia." However, we were aware that pulmonary haemorrhage, a common complication of neonatal cold injury (Mann and Elliott, 1957; Bower, Jones, and Weeks, 1960) could not be excluded as a cause of the crepitations. Pathological changes in the lungs were found in all five cases on whom necropsies were performed. There was either foci of atelectasis, or congestion of alveolar capillaries, or intra-alveolar haemorrhage, or frank bronchopneumonia.

TABLE I.—*Group A*—11 *Infants Treated with Corticosteroids or A.C.T.H.*

Case No.	Birth Weight lb. oz.	Birth Weight g.	Day of Onset of Sclerema	Associated Clinical Features	Antibiotics	Hormone Total Dose	Result	Post-mortem Findings and Remarks
1	2 6½	1,090	2	Mother had positive Wassermann test	Pen.	Hydrocortisone 75 mg.	Died	Lungs: Foci of atelectasis. Gangrene in toes of left foot. Skin and subcutaneous tissue, normal
4	2 10	1,190	11	Vomiting day 5. Cyanotic attacks day 10	Pen.	Hydrocortisone 150 mg.	,,	Blood sugar: 61 mg. day 1; <10 mg. day 3
5	3 5	1,500	9	Hyperbilirubinaemia. Diarrhoea and dehydration	Pen. Chloro.	Hydrocortisone 200 mg.	,,	Lungs: Foci of atelectasis and congestion of alveolar capillaries. Liver: Bile stasis. Skin and subcutaneous tissue normal
6	3 15	1,785	16	Gastroenteritis and dehydration. Cyanotic attacks	Pen. Strep. Chloro.	Hydrocortisone 100 mg.	,,	Lungs: Confluent bronchopneumonia and foci of atelectasis. Liver and large bowel: moderate congestion
8	3 0	1,360	2	Hypothermic. Rectal temp. 90° F. (32·2° C.)	Nil	A.C.T.H. 60 units	,,	—
9	4 15½	2,250	2	Hypothermic	Pen. Strep.	Hydrocortisone 75 mg.	,,	—
12	2 8	1,135	2	Regurgitation through the nostrils. Later blocked nose	Pen. Strep.	Hydrocortisone 275 mg.	,,	Sclerema resolved before sudden death on day 8
13	3 5	1,500	12	Hyperbilirubinaemia. Frequent stools. Creps both bases	Pen. Strep.	Hydrocortisone 50 mg.	,,	Lungs: Bronchopneumonia, intra-alveolar haemorrhage, and atelectasis
14	2 9	1,160	1	Hypothermic. Rectal temp. 88° F. (31·1° C.)	Nil	Hydrocortisone 100 mg.	,,	—
18	3 14	1,760	2	Hyperbilirubinaemia. Vomiting; blood-stained stools. Dehydration	Pen.	Hydrocortisone 175 mg.	,,	Lungs: Acute inflammatory exudate in alveoli, other alveoli filled with blood. Brain: Large haemorrhage around cerebellum. Liver: Hydropic degeneration of parenchymal cells. Adrenal: Agonal haemorrhage. Skin and subcutaneous tissue normal
21	2 10½	1,205	3	Blocked nose. Thrush	Pen.	Hydrocortisone 175 mg. A.C.T.H. 30 units	Alive	Sclerema of cheeks and legs; resolved in 4 days (see text)

Pen. = Penicillin. Strep. = Streptomycin sulphate. Chloro. = Chloramphenicol.

In this group one infant (Case 21) survived. This baby, whose birth weight was 2 lb. 10½ oz. (1,205 g.), was admitted to the ward with a rectal temperature of 87°F. (30.6°C.). Three days later mild sclerema was noted on the cheeks and legs, the rectal temperature then being 96°F. (35.6°C.). Treatment was started with hydrocortisone and penicillin. The sclerema was much less 48 hours later and had disappeared by the fourth day of treatment. Hydrocortisone was given for five days, and this was followed by three daily injections of A.C.T.H. each of 10 units. The baby was discharged quite well after 47 days in hospital.

There was resolution of the sclerema in one other infant (Case 12), but it died on the eighth day of life. Necropsy was not carried out.

Table II summarizes the clinical findings and the outcome of the 14 infants in group B who received no corticosteroid hormones. Their birth weights ranged from 1 lb. 15½ oz. to 8 lb. 14 oz. (895 to 4,030 g.). Of these infants, six were less than 3 lb. (1,360 g.) in weight, while three weighed more than 5½ lb. (2,500 g.).

The most common associated illness in the infants was "bronchopneumonia" and two infants had passed blood-stained stools. Necropsies were carried out on only two of the 11 babies who died. In both instances the lungs showed some degree of intra-alveolar haemorrhage with or without frank evidence of bronchopneumonia. In addition, one child developed gangrene of the toes and haematuria resulting from a thrombus in the descending aorta and left renal artery.

legs, when the rectal temperature was 97.6° F. (36.4° C.). This disappeared 24 hours later without any special treatment. The child required two exchange transfusions for hyperbilirubinaemia on the sixth and seventh days of life. He was discharged fully breast-fed on the 26th day.

One other infant (Case 24) had sclerema of the cheeks which resolved without any specific therapy. However, this baby, whose weight fell to 1 lb. 11 oz. (765 g.), died on the 10th day of life.

TABLE II.—*Group B*—14 *Infants Treated without Corticosteroids*

Case No.	Birth Weight lb. oz.	Birth Weight g.	Day of Onset of Sclerema	Associated Clinical Features	Anti-biotics	Result	Post-mortem Findings and Remarks
2	2 6	1,075	2	Cyanotic attacks; vomited feeds	Nil	Died	Lungs: Acute inflammatory exudate in alveoli and bronchioles; areas of atelectasis and intra-alveolar haemorrhage. Liver: mild fatty change. Skin and subcutaneous tissue: normal
3	4 13	2,185	13	Creps and bronchial breathing left lung. Blood-stained stools terminally	Pen. Strep.	,,	—
7	7 3½	3,275	5	Badly asphyxiated at birth. Tachypnoea. Creps both lungs	Pen. Strep.	,,	—
10	2 2	965	2	Hypothermic. Rectal temp. 90·6° F. (32·6° C.). Creps left lingula	Pen.	,,	—
11	2 7	1,105	1	—	Nil	,,	—
15	Not known		11	Hypothermic. Rectal temp. 85° F. (29·5° C.). Dyspnoea and cyanosis	Pen. Strep.	,,	—
16	1 15½	895	2	—	Nil	,,	—
17	3 12	1,700	1	Blood-stained stools. Creps both lungs	Pen.	,,	—
19	6 0 On admission	2,720	46	Salmonella enteritis. Dehydration. Marasmus	Chloro. Pen.	Alive	See text for details
20	8 14	4,025	12	Badly asphyxiated at birth. Dehydration. Creps right lung. Septic umbilicus. Gangrene of toes	Pen. Chloro.	Died	Lungs: Marked congestion; some intra-alveolar haemorrhage. Thrombosis of aorta and left renal artery. Renal infarction. Liver: congestion of sinuses
22	4 4½	1,940	2	Hyperbilirubinaemia. Hypothermic. Rectal temp. 89° F. (31·7° C.)	Nil	Alive	Sclerema of buttocks, thighs, and legs resolved in 2 days (see text)
23	2 12	1,245	7	Vomiting. Dehydration. Creps right lung	Pen. Strep.	Died	—
24	2 3	995	2	Hypothermic. Temp. 90° F. (32·2° C.). Jaundice. Sudden vomit and collapse on day 10	Nil	,,	Sclerema of cheeks resolved in 3 days
25	4 1	1,845	4	Hypothermic. Cyanosis. Bilateral conjunctivitis	Pen.	Alive	Sclerema resolved in 24 hours (see text)

Pen. = Penicillin. Strep. = Streptomycin sulphate. Chloro. = Chloramphenicol.

Brief case histories of the survivors in group B are given.

Case 19.—A male infant, 34 days old and weighing 6 lb. (2,720 g.), was admitted suffering from a salmonella enteritis and failure to thrive. Sclerema developed eight days after admission, first on the legs and later on the buttocks, upper limbs, and cheeks. The onset of the sclerema was associated with a recurrence of diarrhoea and dehydration. Before the starting of intravenous therapy the serum sodium level was 127 mEq/l., the plasma chloride level was 111 mEq/l., and the carbon dioxide content was 5.0 mEq/l. The blood urea level was 206 mg./100 ml. Apart from intravenous replacement of fluid loss, the child was given chloramphenicol orally in doses of 125 mg. every six hours as well as penicillin in doses of 250,000 units every eight hours by intramuscular injection. The sclerema regressed on this treatment and disappeared six days later. However, this infant failed to gain weight because he ruminated. Gain in weight occurred when the feeds were thickened with cereals. When seen again at the age of 7½ months the child weighed 14 lb. 9 oz. (6.6 kg.) and he appeared to be thriving.

Case 25.—This infant, one of twins, weighed 4 lb. 1 oz. (1,845 g.) at birth. On the second day of life the rectal temperature had fallen to 93° F. (33.9° C.). Sclerema of the legs, forearms, and back was observed on the fourth day, when the child's rectal temperature was 98.4° F. (36.9° C.). The only form of treatment was penicillin by intramuscular injection in doses of 100,000 units every eight hours. Signs of sclerema had disappeared 24 hours later, when the only abnormality noted was a bilateral conjunctivitis. The infant began to gain weight after the eighth day of life and was discharged from the ward on the 26th hospital day.

Case 22.—A male premature infant weighing 4 lb. 4½ oz. (1,940 g.) was admitted from the district. Rectal temperature on admission was 89° F. (31.7° C.). By the third day of life patchy sclerema had developed on the buttocks, thighs, and

Discussion

Table III shows that both groups were well matched with regard to the premature infants including those below 3 lb. (1,360 g.) in weight, and the extent of the sclerema and the associated illnesses. The groups differed in that all three full-term infants were in group B, which also contained more patients who received no antibiotics.

The mortality was high in both groups, and there was no significant difference between the patients treated with or without corticosteroids. Most of the 17 cases recorded in the literature that were successfully treated with cortisone or A.C.T.H. were isolated cases, and it is possible that only the successes and not the failures were published.

Before 1948 only full-term babies with sclerema appear among the reported survivors. Six premature infants are included among the cases treated successfully

TABLE III.—*Comparison of* 25 *Infants in Groups A and B*

	Group A (Hormones)	Group B (No Hormones)
Total number	11	14
Premature infants	11	11
Birth weight <3 lb. (1,360 g.)	6	6
Full-term infants	0	3
Extensive sclerema	10	10
Survivors	0	1
Mild sclerema	1	4
Survivors	1	2
Antibiotics	9	9
No antibiotics	2	5
Associated illnesses:		
Respiratory	6	7
Gastro-intestinal	3	3
Others	4	6
Survivors	1	3

with corticosteroids (Kendig and Toone, 1951 ; Kendall and Ledis, 1952 ; Eisenoff *et al.* 1954 ; Glynn Williams, 1953 ; Kurzrok *et al.*, 1954). It might therefore be argued that premature infants with sclerema can now be saved with corticosteroids. However, in our series premature infants have survived without the use of these hormones.

The use of antibiotics might influence the course of sclerema neonatorum. Bower *et al.* (1960) had 9 survivors among 14 full-term infants with sclerema and cold injury who received antibiotics without the addition of adrenal steroids. Fairchild (1955), in commenting on a report of Buess, who treated three full-term infants successfully with cortisone and antibiotics, stated that " the incidence of increased cures comes at a time when antibiotics are used more frequently in the newborn period." Wickes (1956) in reporting the case of an infant with sclerema who survived after the use of cortisone and tetracycline, admitted that antibiotics played their part, but felt that improvement coincided with the hormone therapy. This investigation was not designed to test the efficacy of antibiotic therapy and no definite conclusions regarding its value can be drawn from our series.

The percentage of body surface affected by the sclerematous process seemed to influence the prognosis. Whereas there was only one survivor (full-term) among the 20 cases with extensive sclerema, three of the five premature infants survived when not more than three different areas of the body were involved. Of these latter babies, two received no hormonal therapy.

It might be expected that the prognosis of sclerema neonatorum would be better in full-term than in premature infants, and it is of interest that the only survivor in our series with extensive sclerema was a full-term baby.

Thus on the basis of our study and a critical review of the literature we conclude that there is as yet no certain evidence that corticosteroids are of value in the treatment of sclerema neonatorum.

Summary

The efficacy of treatment of sclerema neonatorum with or without hydrocortisone or A.C.T.H. was assessed in a series of 25 infants.

Of 11 children treated with hydrocortisone or A.C.T.H there was remission of the sclerema in two cases. In a control group of 14 infants not receiving these hormones, there were three survivors.

The prognosis is influenced by the extent of the sclerematous process.

We thank Dr. I. Frack, hospital superintendent, for permission to publish. We are indebted to Dr. E. Kahn, who suggested this investigation and who gave invaluable criticism and advice. Dr. S. Wayburne kindly allowed us to study some of the patients who were admitted under his care. Our thanks are also due to Dr. C. Isaacson and his staff, of the South African Institute for Medical Research, who carried out the post-mortem examinations.

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CUSHING'S SYNDROME IN CHILDHOOD DUE TO ADRENAL HYPERPLASIA

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Cushing's syndrome is rare in childhood. All the cases reported in children under 10 years of age have been due to an adrenal tumour, except four which were associated with adrenocortical hyperplasia. Chute, Robinson, and Donohue (1949) first reported a case in which the syndrome was not due to a tumour, in an 8-year-old girl who died post-operatively after partial adrenalectomy. Hubble and Illingworth (1957) described two examples of adrenal hyperplasia in children. One of these was an 8-year-old boy with Cushing's syndrome who presented with arrested growth. He was treated by adrenalectomy ; seven-eighths of the left and the whole of the right adrenal were removed. He afterwards required maintenance therapy by cortisone and grew rapidly. Goldblatt and Snaith (1958) described a case in an infant, and Silver and Ginsburgh (1960) described another in an 8-year-old girl. Both these cases were treated by bilateral adrenalectomy in two stages.

We now report a case of Cushing's syndrome due to adrenocortical hyperplasia, with onset at age 9, in a boy who was treated with total bilateral adrenalectomy when he was 11 years old.

Case History

The patient was referred to hospital at the age of 10 years 2 months with a history of excessive gain in weight for one year. Previously he had been rather thin, with a poor appetite. His mother had noticed that he had stopped growing. He also had a history of periodic pain and pyrexia. On examination he was found to be obese, weight 121 lb. (54.9 kg.), height 55 in. (140 cm.), B.P. 145/112. He had a slight buffalo hump but no striae. He was put on a 1,000-calorie diet, to which he strictly adhered. During the next four months he lost 14 lb. (6.4 kg.) in weight and his blood-pressure fell to 125/95. In this period he developed frontal and temporal headaches and also complained of pains in the back, of increasing severity. There was a marked increase in growth of body hair.

On October 6, 1958, when he was aged 10 years 8 months, he was admitted to hospital for investigation.

Clinical Findings

He was a plethoric moon-faced boy with acne on the forehead. The sides of his face and neck and his back were covered with fine hair. His pubic and axillary hair had developed, his penis and testes were still small. He now had a marked buffalo hump and showed the characteristic appearances of Cushing's syndrome (Fig. 1). His B.P. was 130/105, Hb 14.9 g./100 ml., W.B.C. 9,100, eosinophils nil. Fasting blood sugar was 89 mg./100 ml. Glucose tolerance: after 40 g. glucose the blood sugar rose to 177 mg./100 ml. in two hours. The blood sugar showed a normal response to the insulin-sensitivity test, using 4 units of soluble insulin intravenously. Serum sodium, potassium, chloride, calcium, and blood urea were normal. Urine: albumin nil, deposit normal, culture sterile. The 24-hour urinary output of 17-ketosteroids was 53.1 mg., of 17-hydroxycorticosteroids 60 mg., of creatinine 0.325 g., and of creatine 0.258 g. Patterson's (1947) test for dehydroisoandrosterone was negative. The adrenal suppressing effect of 9α-fluoro-16-α-hydroxyprednisolone was then determined (Table I).

Triamcinolone (4 mg. four times daily) reduced the urinary 17-ketosteroids from 53.1 to 28.2 mg./24 hours after eight days' treatment, and to 24.7 mg./24 hours after 16 days' treatment. The 17-hydroxycorticosteroids were reduced from 60 to 49.5 mg./24 hours after eight days' treatment. After three weeks of triamcinolone there was no further fall in these urinary steroids. There was no improvement in the boy's symptoms on this treatment.

Dr. E. E. Hill (Department of Clinical Endocrinology, Birmingham), using the Morris method for fractionation of the total 17-ketogenic steroids into 11-desoxy and 11-oxygenated 17-ketogenic steroids (Morris, 1959), reported that the 17-ketogenic steroids were high for a child of this age (Table II), but, unlike congenital adrenal hyperplasia and virilism, the ratio of the 11-desoxy/11-oxygenated ketogenic steroids was normal (Hill, 1960).

X-ray films of the spine showed generalized osteoporosis. His skeletal age was approximately 10 years. An intravenous pyelogram was normal. Both kidneys were in the normal position and there was no evidence of suprarenal calcification. Perirenal insufflation of air (Dr. W. E. C. Astle): no suprarenal tumour was demonstrated; the left suprarenal was visualized and the appearances were consistent with slight hyperplasia; the right suprarenal was not visible.

The case was then shown to Professor D. V. Hubble, who confirmed that this was Cushing's syndrome, caused by adrenal hyperplasia, and suggested total adrenalectomy. Before carrying out such a drastic operation it was decided to watch the boy's progress for a time. During the next three months, however, he deteriorated. The pains in his back were more acute and he became weaker and more miserable. *X*-ray examination of the spine showed collapse of the twelfth thoracic and first lumbar vertebrae due to osteoporosis.

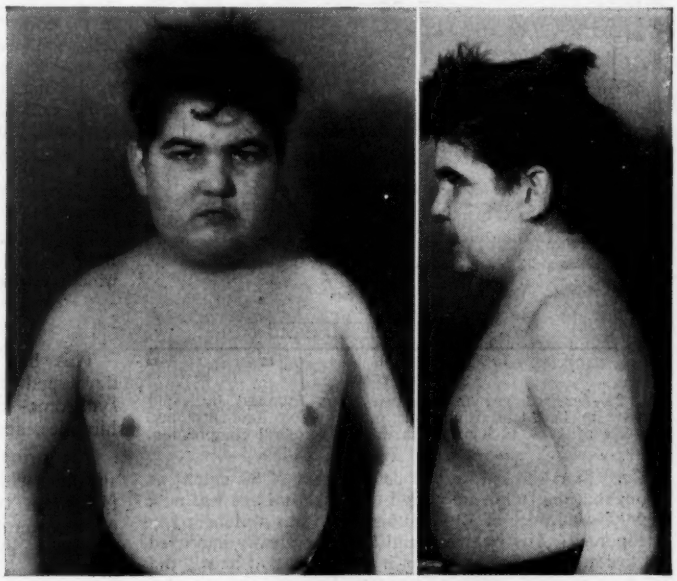

FIG. 1.—Appearance before adrenalectomy.

On March 13, 1959, he was readmitted for adrenalectomy. His blood-pressure was then 190/120–160/130. The effect of A.C.T.H. was tested two weeks before operation (see Table I). Treatment with A.C.T.H. gel (40 I.U. b.d.) for two days increased the output of 17-ketosteroids from 30.5 mg. to 91 mg./24 hours, and the 17-hydroxycorticosteroids from 79.7 mg. to 220 mg./24 hours.

TABLE I.—*Excretion of Urinary Steroids*

Date	Treatment	17-Keto-steroids (mg./24 Hours)	17-Hydroxy-corticosteroids (mg./24 Hours)
9/10/58	Nil	53·1	60·0
29/10/58	After 8 days triamcinolone 16 mg./day	28·2	49·5
5/11/58	After 16 days triamcinolone 16 mg./day	24·7	—
12/11/58	On triamcinolone 12 mg./day	26·3	48·7
15/3/59	Nil	48·1	108
16/3/59	"	30·5	79·7
17/3/59	A.C.T.H. gel 40 I.U. × 2	51·8	195
18/3/59	" " " "	91	220
19/3/59	Nil	27·3	170
20/3/59	"	35·8	116
2/4/59	Bilateral adrenalectomy		
	Maintenance therapy		
22/4/59	Cortisone 62·5 mg./day	1·7	26·7
8/1/60	Cortisone 12·5 mg./day. Fludrocortisone 0·1 mg./day	1·6	7·8

TABLE II

11-Desoxy Fraction II	11-Oxygenated Fraction III	Ratio II/III
6 mg./24 hours	14·8 mg./24 hours	0·4
5·6 "	18·2 "	0·3

Operation

A diagnosis of Cushing's syndrome due to adrenal hyperplasia having been established, an operation was carried out by one of us (G.G.C.) on April 2, 100 mg. of cortisone having been given intramuscularly two hours before operation. The incision used was the anterior transverse upper abdominal approach. The right adrenal was mobilized first, and this was carried out satisfactorily, 50 mg. of hydrocortisone again being given intravenously while the gland was being completely removed. The left adrenal was then removed completely, 50 mg. of hydrocortisone again being given intravenously; but this dissection was complicated by some haemorrhage from rupture of the left adrenal vein at its junction with the left renal vein. When this happened his blood-pressure fell to 30 mm., but when the haemorrhage was controlled it rose immediately to 130 mm. The abdomen was closed in layers.

Post-operatively a further 100 mg. of cortisone was given the same day, making a total of 300 mg. This dose was continued for the next two days and then gradually reduced

over the next four weeks to 12.5 mg. daily. He continued to have hypertension (B.P. 130/100–160/100) for four weeks after operation. His blood-pressure then slowly fell to 115/75.

Progress

From the second week post-operatively there was a steady improvement in his appearance and general condition. He gradually lost his hirsuties and obesity. Three months after adrenalectomy he seemed years younger and looked like a normal boy of 11. He started to grow four months after operation and gained 4½ in. (11.4 cm.) in six months, and 9½ in. (24 cm.) in 18 months (Fig. 2).

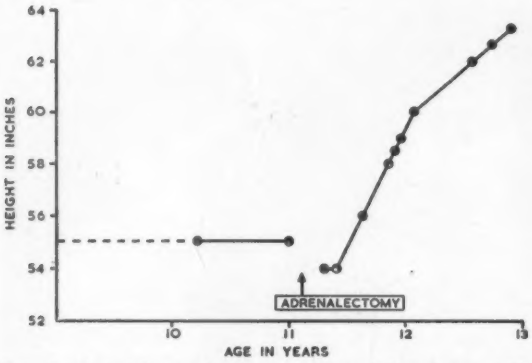

FIG. 2.—Arrested growth for two years followed by rapid increase in height, starting four months after adrenalectomy. The fall of 1 in. (2.5 cm.) was due to vertebral compression.

X-ray films showed normal development of his epiphyses throughout the follow-up period. His skeletal age was now slightly in advance of 13 years and there was no longer any osteoporosis. His weakness and lassitude greatly improved but five months after operation it was noted that he still did not have as much energy as a normal boy, and that he tired easily in hot weather in spite of extra salt in his diet. He was then given fludrocortisone (9α-fluorohydrocortisone) 0.1 mg. daily, in addition to cortisone. This produced a great improvement. After trying various dose levels it was found that doses of cortisone 15 mg. daily and fludrocortisone 0.1 mg. daily were satisfactory in maintaining normal health and blood-pressure.

A year after operation he was leading a normal vigorous life and could cycle 10 miles (16 km.) without fatigue (Fig. 3). At the time of writing he had been followed up for two years and remained fit and well.

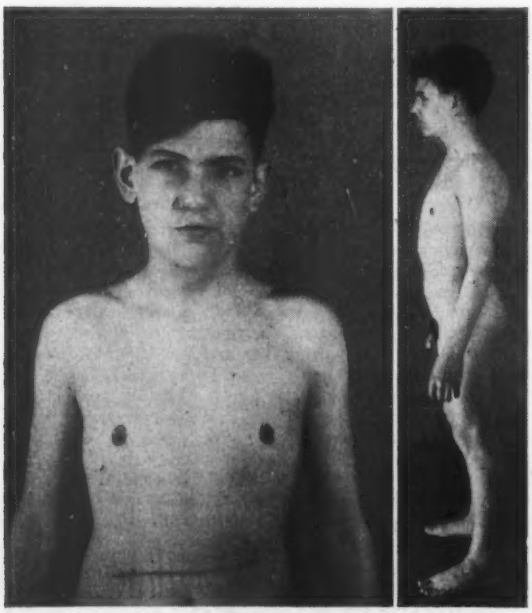

FIG. 3.—Appearance 11 months after adrenalectomy.

Histology

Professor T. Symington kindly examined the H. and E. sections and reported that the appearances show a prominent zona glomerulosa on the surface of the gland, while the rest of the cortex forms a fairly uniform picture. Most of the cells are compact in type—that is, eosinophilic cytoplasm—some of them are vacuolated and obviously contain lipid material. These appearances of eosinophilic compact cells, extending almost the whole length of the zona fasciculata, are more like that found in the adrenogenital syndrome than that usually found in the hyperplastic gland from a case of Cushing's syndrome, but a similar picture can be obtained from Cushing's syndrome if the gland is removed after A.C.T.H. treatment or after death.

The glands, which were obviously much enlarged, were not weighed, as it was hoped to carry out enzyme studies, which eventually was not practicable.

Discussion

This boy stopped growing at the age of 9 and developed the characteristic picture of Cushing's syndrome—obesity with moonface and buffalo hump, hirsuties, acne, osteoporosis, and marked hypertension.

The urinary 17-ketosteroids and 17-hydroxycorticosteroids, which were both very high, showed a marked fall when triamcinoline was given. The suppression of exaggerated adrenocortical activity by exogenous steroids is characteristic of adrenal hyperplasia and not of a tumour (Wilkins, 1957). When hyperplasia is associated with the adrenogenital syndrome, in which there is excess of corticotrophin due to defective synthesis of cortisol, the suppression by exogenous steroids is complete and the urinary 17-ketosteroids return to normal (Jailer, Gold, and Wallace, 1954). Similarly, in Cushing's syndrome suppression also occurs when adrenal hyperplasia is present (Cope, 1956). This probably indicates that the adrenal hyperactivity is under the control of corticotrophin stimulation (Cope and Harrison, 1955). However, in our case the adrenal suppression was incomplete after three weeks of steroid therapy, and the urinary 17-ketosteroids were 26.3 mg. and the 17-hydroxycorticosteroids 48.7 mg./24 hours. The dose of triamcinoline was adequate to have produced corticotrophin suppression, but despite this excessive adrenocortical activity continued. This presumably indicates that the overactivity of the adrenal cortex was in some degree independent of corticotrophin control.

There was a great increase in adrenocortical activity as soon as A.C.T.H. was given, and the urinary 17-hydroxycorticosteroids rose 220 mg. on the second day. This response to exogenous A.C.T.H. stimulation suggests that the adrenal cortex was not under maximal stimulation by corticotrophin. When the adrenals were removed, two weeks after A.C.T.H. had been given, they showed microscopical changes resulting from this stimulation by A.C.T.H.—that is, eosinophilic compact cells extending from the zona reticularis along almost the whole length of the zona fasciculata. These changes in the hyperplastic adrenals in Cushing's syndrome, if the glands have been removed after A.C.T.H. therapy,

have previously been recorded (Symington *et al.*, 1958; Symington, 1959). The microscopical appearances in fact resembled those found in the adrenogenital syndrome, in which condition there is an excess of corticotrophin. It has been suggested that Cushing's syndrome may be due to hypersensitivity of the adrenals to corticotrophin, which is not present in excessive amounts (Christy, Wallace, and Jailer, 1955).

A raised urinary pregnanetriol is characteristic of adrenal hyperplasia due to the adrenogenital syndrome. In this case, however, the mean ratio of the 11-desoxy/11-oxygenated ketogenic steroids was 0.35 (Table II), which is normal. The ratio of these fractions in the adrenogenital syndrome is much higher and averages 2.3 (Hill, 1960).

The responses to 9α-fluoro-16α-hydroxyprednisolone and A.C.T.H., together with the negative Patterson test for dehydroisoandrosterone, indicated that this boy was suffering from adrenocortical hyperplasia and not from an adrenal adenoma or carcinoma.

The prognosis in Cushing's syndrome due to adrenocortical hyperplasia recorded in adults is bad and the average expectation of life without treatment is about five years (Bishop, 1954). Bilateral total adrenalectomy is the treatment of choice, and in our opinion the anterior transverse upper abdominal approach is a highly satisfactory one for this procedure (Aird and Helman, 1955). Partial adrenalectomy is unreliable, as the patients are apt either to relapse or to require maintenance cortisone, anyway, in order to prevent adrenal crises.

The results of total adrenalectomy on this boy have been most satisfactory and he has been very well for the past 20 months on small maintenance doses of cortisone and fludrocortisone. He now has the normal appearances and vigour of a boy of 12. His genitalia are developing with puberty, which seems to be taking place normally. He started to grow four months after adrenalectomy and he now shows a pubertal spurt of growth.

Summary

A case of Cushing's syndrome due to adrenocortical hyperplasia developing in a 9-year-old boy is described, in which the presenting symptoms were obesity and arrested growth.

He was treated successfully by total bilateral adrenalectomy through a transabdominal incision.

The diagnostic tests differentiating this condition from adrenal tumour are described, and the results compared with those found in the adrenogenital syndrome. A follow-up report is given over two years, with particular reference to growth and development.

We thank Professor D. V. Hubble for his help and encouragement in presenting this case, and Professor T. Symington for his report and explanation of histological sections. We are grateful to Dr. E. C. Butterworth, of the Biochemistry Department of the North Staffordshire Royal Infirmary, for the urinary steroid estimations, and to Dr. E. E. Hill and the Department of Clinical Endocrinology, Birmingham, for the fractionation of 17-ketogenic steroids. We also acknowledge the help of Dr. W. E. C. Astle and Dr. G. Anderson with the radiology, and Dr. L. Bowcock for the photographs.

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Preliminary Communications

An Isotope Test of Calcium Absorption *

At the present time the measurement of calcium absorption requires full calcium balance procedures. A valid calcium balance takes at least three or four weeks to perform and the determination of the state of calcium absorption in any individual subject is therefore time-consuming and costly. It is probably fair to say that many of the problems of calcium absorption remain unsolved largely because of the technical difficulties involved in their study.

The availability of radioisotopes of calcium and strontium, and in particular the availability of calcium-47, which is a γ-emitting isotope with a relatively short half-life, suggested the possibility that a simple isotopic procedure might be developed for the measurement of calcium absorption. The fate of ingested isotopes of calcium and strontium has been studied (Staub, 1954; Blau *et al.*, 1954; Bronner and Harris, 1956; Samachson, 1960), but no standardized test procedure has been established. The present paper describes a simple isotopic procedure for estimating calcium absorption based on plasma activity two hours after oral administration of the isotope.

METHODS

The isotope was usually given with 250 mg. of calcium as calcium chloride not less than one hour after the last meal; no further food was allowed for at least one hour after the oral dose had been given. Some concentrated orange juice was also given to render the mixture more palatable. Samples of venous blood were taken at intervals after the administration of the dose, and the plasma activity was determined and expressed as a percentage of the dose per litre of plasma. In a few cases the isotope was given with calcium carbonate carrier. The isotope was equilibrated for 24 hours with the carrier before administration, and filtration of the material showed that only about 10% of the radioactivity was filterable.

The dose used was 7.5 μc of calcium-47 (half-life 4.7 days) or 5 μc of calcium-45 (half-life 152 days). The calcium-45 was given only to subjects over the age of 40.

*This work was carried out during the tenure of grants from the Medical Research Council, Glaxo Laboratories, and the International Atomic Energy Agency.

With calcium-47, 10 ml. of plasma was counted in a well-type scintillation counter (Harshaw NaI(T1) crystal type 8F8) under such conditions that any contribution to the count rate by scandium-47 was excluded. When the count rates were low the calcium was precipitated from 20 ml. of plasma with an equal volume of saturated ammonium oxalate, and the precipitate was redissolved in concentrated hydrochloric acid and made up to 10 ml. With calcium-45, 10 ml. of plasma was mixed with saturated ammonium oxalate and left to stand for 12 hours. The mixture was then drawn through a filter-paper disk by vacuum filtration and the precipitate washed with saturated ammonium oxalate. The activity in the precipitated film was determined with an automatic end-window Geiger counter (Nuclear Chicago gas-flow detector type D 47 with "micromil" window).

There were 34 normal subjects who were given only calcium-47. They consisted mainly of members of the laboratory and medical staff, but also included a few patients convalescing from acute illnesses. There were 27 cases of osteoporosis as defined by the radiological procedure of Barnett and Nordin (1960); 21 cases of steatorrhoea (11 idiopathic, 8 post-gastrectomy, and 2 pancreatic); and 12 patients receiving steroid therapy for various clinical conditions. The steroid used was prednisolone (7.5–30 mg. daily) or dexamethasone (3–6 mg. daily). There was also one case of Cushing's syndrome.

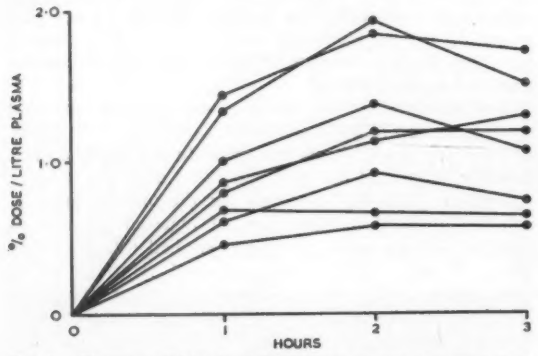

FIG. 1.—Plasma activities in eight subjects at one, two, and three hours after oral administration of calcium-47 chloride.

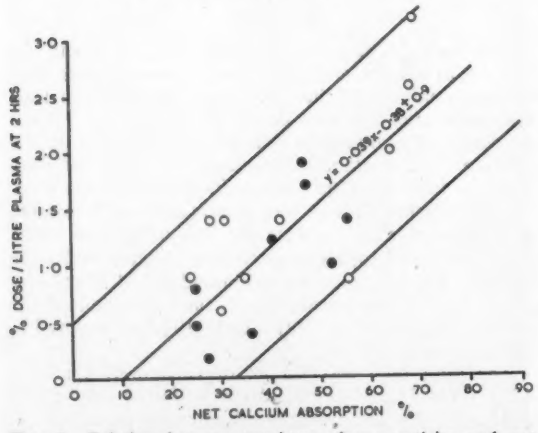

FIG. 2.—Relation between two-hour plasma activity and net calcium absorption on calcium balance in 19 cases. Black dots represent cases in which balance and test were simultaneous. Circles represent cases in which the balance had been performed some time before the isotope test.

RESULTS

In the first eight normal subjects the blood was taken hourly for three hours and the results obtained are shown in Fig. 1. The activity in the plasma rose slightly in the first and second hours and then remained steady or fell slightly in the third hour. On the basis of these results the two-hour blood activity was selected as the significant value.

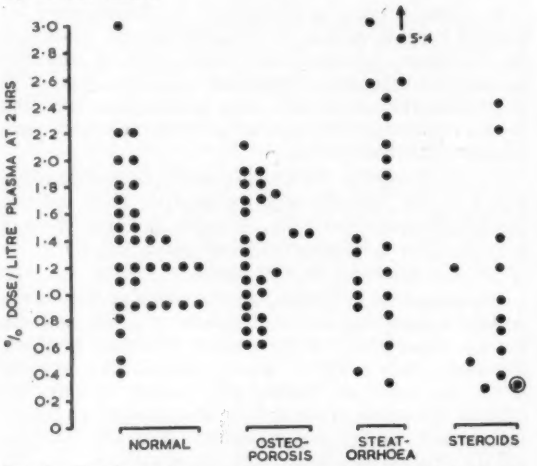

FIG. 3.—Two-hour plasma activities in various diagnostic groups.

Absorption tests were carried out on nine subjects in whom calcium balances were being performed at the same time and in 10 in whom balances had been done within the previous year. The net absorption of calcium calculated from the calcium balance is compared with the isotope test in Fig. 2, which indicates that there was a reasonably good agreement between the two procedures (correlation coefficient $=0.78$; $P<0.01$). The regression line of the plasma activity on the net absorption is: $y=0.039x-0.38$ and the 95% confidence limits are $\pm 0.9\%$ of the dose per litre. If only those cases are considered in which the isotope tests were carried out during the balance, the 95% confidence limits are reduced from ± 0.9 to $\pm 0.7\%$ dose per litre of plasma.

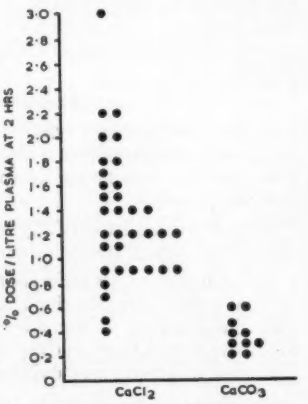

FIG. 4.—Two-hour plasma activities in normal subjects given calcium-47 in calcium chloride carrier (left) and in calcium carbonate carrier (right).

The results of absorption tests in 34 normal subjects, 27 cases of osteoporosis, 21 cases of steatorrhoea, 12 patients on steroid therapy, and one case of Cushing's syndrome are shown in Fig. 3. The two-hour plasma activity in the normal subjects extended from 0.4 to 3% of the dose per litre. The range of values observed in the cases of osteoporosis was essentially the same. In the cases of steatorrhoea the results extended right across the normal range, but there were no cases of untreated osteomalacia in this group. There was no apparent relationship between plasma activity and post-gastrectomy or idiopathic

steatorrhoea, but it may be worthy of note that the two lowest values obtained were in cases of pancreatic steatorrhoea.

In patients on steroid therapy the plasma activity ranged from 0.3 to 2.3% per litre, but all except two were below 1.4%. The two highest values were obtained in one patient who had been on steroids for only two weeks and in another on 7.5 mg. of prednisolone a day. The lowest value observed was in the case of Cushing's syndrome.

Ten subjects were given calcium-47 carbonate instead of calcium-47 chloride. The results of these tests (Fig. 4) indicate that the absorption of isotope in calcium carbonate carrier was inferior to its absorption in calcium chloride.

DISCUSSION

The procedure we have described is simple and quite suitable for out-patient use. Its validity depends upon the relationship between the two-hour plasma activity and the net calcium absorption calculated from the balance data. The observed correlation warrants the view that the isotopic procedure provides an index of calcium absorption. The 95% confidence limits are rather wide, but we have shown that it is partly accounted for by the long interval (up to one year) between some of the tests and the balances. Even when these latter tests are included the agreement is close enough to suggest that calcium absorption is a fairly constant factor in any given individual. The relatively wide normal range is therefore presumably not a function of the isotopic procedure as such but reflects the wide range of calcium absorption in normal subjects.

The results obtained in osteoporosis are entirely compatible with the results of our balance studies in this type of case (Nordin, 1960), which have shown that the great majority of patients with osteoporosis absorb calcium normally.

The results obtained in steatorrhoea may appear surprising since lower plasma activities might have been expected. However, this is a heterogeneous group of cases, many of them on treatment, and does not include any cases of untreated osteomalacia. Our balance studies (Nordin, 1961) have shown that the faecal calcium content in cases of steatorrhoea is slightly higher than that of normal subjects at the same intake levels, but the difference is a relatively small one.

The results obtained in patients on steroid therapy are also compatible with our own previous observations and with those of other workers (Bunim *et al.*, 1958; Slater *et al.*, 1959). On moderate doses of corticosteroids the only consistent abnormality of calcium balance so far observed is an impairment of calcium absorption. It would be compatible with the view that osteoporosis is caused by negative calcium balance to suggest that this malabsorption of calcium is at least a factor in the pathogenesis of steroid osteoporosis.

The isotopic procedure lends itself to the large-scale comparison of the absorption of different calcium compounds. So far we have only tested the absorption of calcium carbonate, which is of particular interest because of its use in the fortification of bread. The results suggest that calcium carbonate may be less well absorbed than calcium chloride, but clearly further work is required.

In conclusion, we suggest that this simple procedure may lend itself to the study of calcium absorption on a much larger scale than is possible with conventional balance techniques.

E

SUMMARY

Calcium-47 in 250 mg. of calcium chloride was given to 34 fasting normal subjects. The maximum plasma activity was reached about two hours later and ranged from 0.3 to 3% of the dose per litre of plasma.

There was a good correlation between the two-hour plasma activity and the net calcium absorption as determined by calcium balance in 19 subjects ($r=0.78$; $P<0.01$).

Cases of osteoporosis and of steatorrhoea and patients on steroid therapy were also studied; absorption by most of those on steroid therapy was low.

Absorption of the isotope appeared to be reduced when it was given in calcium carbonate carrier.

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Medical Memoranda

Visceral Scleroderma Without Skin Involvement

Only two reports of visceral scleroderma without skin involvement have been found in the literature. In the following case the patient presented with persistent vomiting, but there were no skin changes suggestive of scleroderma, and the diagnosis was not suspected in life or at necropsy. However, the histological examination of the heart, lungs, and alimentary tract showed changes characteristic of visceral scleroderma.

CASE REPORT

The patient, a man of 20, gave a history of persistent vomiting, almost every day for a year, with consequent loss of weight and, in the last month, generalized prostration. No other suggestive symptoms could be elicited by systematic questioning.

On examination he was grossly emaciated and too weak to sit up. His blood-pressure was 70/50 and his pulse irregular, but no abnormality was found on clinical examination in any other system.

An *x*-ray film of the chest taken at the bedside was unhelpful. An electrocardiogram showed multiple ventricular extrasystoles. Plasma electrolyte determinations gave the following results: sodium 135 mEq/l., potassium 3.5 mEq/l., chloride 71 mEq/l. Blood urea was 89 mg./100 ml. Total serum albumin was 3.4 g./100 ml., and globulin 1.6 g./

100 ml. Electrophoretic strip showed a normal pattern. On his admission the haemoglobin was 117% and the total leucocyte count 6,550/c.mm. (differential count normal).

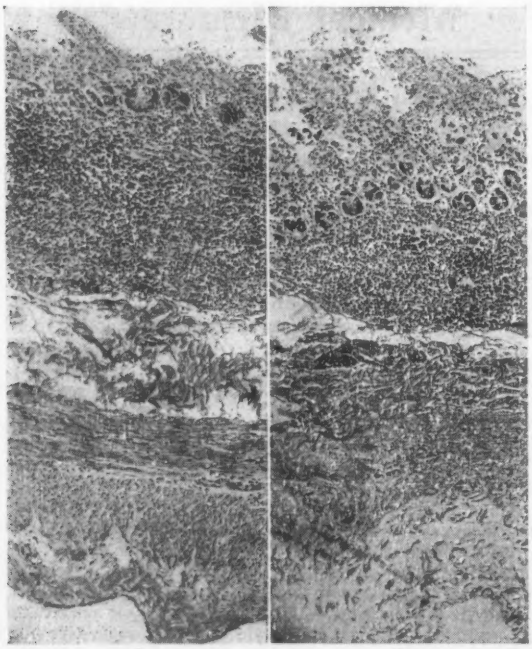
Intravenous fluid was given to restore fluid balance. A Ryles tube was passed and a litre of fluid aspirated from the stomach, although immediately before this the patient had vomited 800 ml. of bile-stained fluid.

A radiograph taken after a small barium meal showed a dilated, atonic duodenum with practically no passage of barium in one hour. After two hours the barium had reached the mid-jejunal region. This investigation suggested ileus of the duodenum and first part of the jejunum, but there was no evidence of actual intestinal obstruction. As we were uncertain whether the ileus was neurogenic, mechanical, or biochemical, it was decided to prepare the patient for a diagnostic laparotomy.

Accordingly, a "polythene" tube was passed into the superior vena cava, and fluids containing high-calorie dextrose, amino-acid, and electrolyte were given. His general condition improved during the next two weeks and he was able to walk around the ward with a portable drip apparatus.

Eighteen days after admission he complained of the onset of sharp right-sided chest pain, worse on inspiration; nine hours later his condition deteriorated and he died unexpectedly.

Necropsy Findings.—The only macroscopic finding of note was dilatation of the first 18 in. (46 cm.) of small intestine. The remainder of the gastro-intestinal tract, the spleen, and other abdominal organs showed no macroscopic abnormality. The histological findings proved to be diagnostic. Sections from jejunum, heart, and lungs are reproduced. Fig. 1 A and B contrast abnormal and normal small bowel, both preparations being from the patient. In the affected section (Fig. 1 A) it can been seen that the muscle layers have been largely replaced by fibrous tissue. Fig. 2 shows lung and pleura with complete obliteration of normal lung architecture by fibrous tissue containing some cystic spaces lined by bronchial epithelium. Fig. 3 shows diffuse myocardial fibrosis. The vessels are normal. Sections from the other organs showed no significant abnormality.



A B

FIG. 1.—Histological sections showing (A) an area of normal small bowel and (B) an abnormal area of small bowel. (×75.)

DISCUSSION

Generalized scleroderma, as emphasized by Prowse (1951), may cause fatal fulminating disease of the bowel, heart, or lungs. Skin involvement has almost universally been reported in published series. The only two reports of visceral scleroderma without skin changes found in the literature are those of Abrams *et al.* (1954) and of Miller *et al.* (1959), and neither paper emphasizes the rarity of this presentation.

There is general agreement that abnormalities of the gastro-intestinal tract occur in approximately 75% of cases of visceral scleroderma (Orabona and Albano, 1958). The characteristic *x*-ray changes are dilatation of the small bowel, especially of the second and third parts of the duodenum and the jejunum. There is also marked delay in the passage of barium (Pugh, 1948). Histologically, the small intestine shows thickening of the submucosa, and fibrosis and atrophy of the muscularis (Beerman, 1948; Bevans, 1945; Boyd *et al.*, 1954).

Electrocardiographic abnormalities reported include conduction defects, T-wave abnormalities, and ventricular extrasystoles (Weiss *et al.*, 1943). Histologically, the myocardium shows fibrotic change; arterial lesions of the myocardium have also been reported (Rottenberg *et al.*, 1959). Pulmonary fibrosis has often been described, and may lead to reduced vital capacity.

In the present case the combination of excessive vomiting, cardiac irregularities, and duodenal ileus

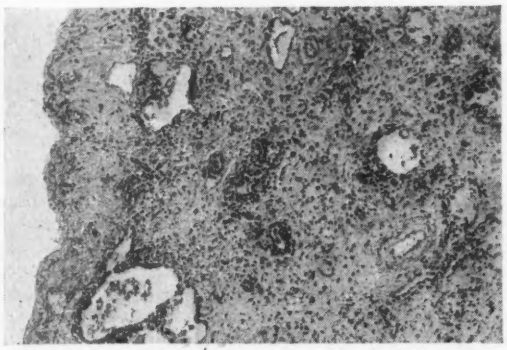


FIG. 2.—Histological section of lung and pleura. (×75.)

FIG. 3.—Histological section of myocardium. (×20.)

should perhaps have led to the diagnosis of visceral scleroderma. The patient's age, however, was unusual, most of the reported cases occurring in patients aged 40 to 60.

I thank Dr. Geoffrey Steed for permission to publish this report, and Dr. J. D. N. Nabarro for his help and encouragement in writing it. The barium-meal examination was carried out by Dr. C. G. Whiteside, radiology department, Middlesex Hospital, and the histological sections were prepared by Dr. John Arthur, Bland-Sutton Institute of Pathology, Middlesex Hospital.

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Acute Left Ventricular Failure after Successful Surgical Treatment of Bleeding Gastric Ulcer

This paper describes the case of a patient with oligaemic shock due to haemorrhage who, immediately after arrest of the haemorrhage, developed left heart failure with pulmonary oedema. The main purpose is to demonstrate that such a new development can take place with dramatic suddenness and that the treatment should be altered diametrically to correspond.

CASE REPORT

A married woman aged 76 was admitted to hospital on February 8, 1961, with a history of having vomited a quantity of bright red blood after experiencing a sudden sharp pain in the upper part of her abdomen. She vomited blood repeatedly and started passing fresh blood per rectum. Her past history revealed that she had suffered "a heart attack" around Christmas, 1960, but otherwise had always been fit and active.

On examination the patient was a thin, pale woman, mentally very active. The pulse was 96 a minute, regular, and of good volume; blood-pressure 160/50. There was evidence of mitral stenosis and aortic regurgitation: not in failure clinically. An E.C.G. showed left ventricular hypertrophy with strain. There was some tenderness in the epigastrium. Dark red blood was passed per rectum. On admission the haemoglobin was 55%.

On account of the history and the evidence of free aortic regurgitation, conservative treatment was decided upon. During the next 18 hours 12 pints (6.8 litres) of blood were given, but repeated haematemeses and melaena were of such extent that she barely held her ground. At this stage it was decided to deal with the problem surgically.

She was taken to the theatre on her bed, with transfusions set up in both arms. Digoxin 0.25 mg. was given before she went to the theatre. On arrival in the anaesthetic room she vomited bright red blood and passed blood and clots per rectum. Rapid induction was performed on the table, and almost immediately she suffered a severe collapse, the carotid pulses being impalpable. The abdomen was quickly opened through an upper midline incision. The stomach was found to be full of blood clot. A high partial gastrectomy was performed in just under 30 minutes, and at the end of operation her condition appeared to be satisfactory in the circumstances. During the operation a total of 1 pint (570 ml.) of blood was transfused. Examination of the specimen revealed an eroded artery in a subacute gastric ulcer. A disturbing factor noted at the conclusion of the operation was the degree of jugular venous distension. A few minutes later, just before her return to the ward, cyanosis developed. Frothy, pinkish fluid appeared at the corners of her mouth and the chest became full of moist sounds. B.P. at the time was 190/60. Oral suction was performed and then a bronchoscope was passed and suction of bronchi continued by this route for 20 minutes—fluid forming as quickly as it was removed.

In view of this acute left and right ventricular failure, aminophylline 0.25 g. was given intravenously and both transfusions were taken down. Esmarch bandages were applied on the suggestion of Dr. K. D. Keele to all four limbs to impede the venous return, thus performing a physiological venesection. At the end of 20 minutes the bronchoscope was removed and suction continued via the oropharynx. After 45 minutes from the onset of symptoms there was a noticeable improvement in the patient's condition. This continued steadily over the next 30 minutes, during which time the necessity for suction became less and the jugular venous engorgement disappeared. The total amount of bronchial aspirations was 2½ pints (1,420 ml.) of frothy blood-stained fluid. The patient was then returned to the ward and placed in an oxygen tent. The limb bandages were released and reapplied at intervals of 30 minutes over the next four hours, until they were finally taken off one at a time, the effect on jugular venous pressure being noted.

The patient made a satisfactory recovery. It is interesting to note that on the first post-operative day her haemoglobin was 87% and haematocrit reading 47; transfusion, therefore, had not been excessive. Her subsequent post-operative progress has been uneventful.

COMMENT

This case raises a number of interesting points: (1) It illustrates a remarkable and dramatic situation where successful surgical treatment of severe haematemesis in a patient with a gross cardiac lesion precipitated an equally serious medical emergency. (2) It demonstrates the swift change from exsanguination to left ventricular failure requiring opposite modes of treatment. (3) It also shows the success of combining bronchial aspiration and medical venesection in the emergency treatment of acute left ventricular failure. (4) With increasing boldness of surgical approach in the treatment of haematemesis in the elderly, particularly those with cardiac lesions, this type of case may not be uncommon.

We thank Dr. K. D. Keele, under whose care this patient was originally admitted, and Mr. O. D. Morris, who performed the operation, for permission to publish this case.

F. T. G. TUFFNELL, M.R.C.S., L.R.C.P., D.A.,
M. F. STRANC, F.R.C.S.,
Ashford Hospital, Ashford, Middlesex.

A scholarship in memory of the late Mr. S. I. Levy has been established by his widow at the Medical School of the Hebrew University of Jerusalem. Mr. Levy was for many years surgeon to the East Ham Hospital and to the Westminster Hospital, and for about 30 years senior surgeon to the London Jewish Hospital. The scholarship will be granted annually to a graduate of the Hebrew University specializing in surgery.

Reviews

GROWTH OF MEDICAL PRACTICE

The Evolution of Medical Practice in Britain. Edited by F. N. L. Poynter. Foreword by W. S. C. Copeman. (Pp. 168+vi 25s.) London: Pitman Medical Publishing Co. Ltd. 1961.

The practice of medicine in the United Kingdom abounds in laws and regulations, and the Society of Apothecaries could have chosen no more topical subject for the first British congress on the history of medicine than the one defined in the title of this book, which contains the papers delivered to it. Rarely have I found so much valuable and interesting information in so few pages, and I recommend every intelligent doctor to study them so that he may judge present and future developments clearly and steadily in the light of what has happened in the past.

In mediaeval times most medical practice was in the hands of the ladies of the manors, their almoners, and "wise women" in the parishes, because monastic institutions were usually in remote districts and leper houses served a very limited purpose. The first recorded intervention by an English government in medical affairs was an Act of 1421 (the ninth year of the reign of Henry V) which gave authority to the Privy Council to restrict practice to adequately trained physicians and surgeons. It had no effect—for the sufficient reason that there were no such persons to do the work. The next was the Medical Act of 1511 (Henry VIII), which forbade anyone to practise without a university degree or a licence from a bishop. The charter of the College of Physicians followed in 1518, but even in London and certainly throughout the rest of the country most licences continued to be granted by the Church.

The Company of Barber Surgeons was legally established in 1540, and two years later came the measure that has been called "The Quacks' Charter," for it permitted "honest persons, as well men as women" to practise without penalty if they gave advice free and were paid only for drugs. This was a frank admission that otherwise the poor would have had no treatment at all. When in 1617 the Society of Apothecaries was formed the apothecaries' claim to prescribe as well as dispense medicines was based on this Act of 1542.

And so the hierarchy of medicine took shape, and the history of the next 300 years tells of the conflict between the interests of physicians, surgeons, and apothecaries. All three had moments of enlightenment when they turned from internecine war to higher things, and there is little doubt that until 1858 it was the apothecaries who afforded the greatest service to the nation. The wisdom with which they managed the training of their apprentices and set the standard of their qualification might profitably be studied to-day by the new professions "ancillary to medicine."

The influence of clinical science, the pharmaceutical industry, health insurance schemes, and medical societies (with a handsome tribute to Sir Charles Hastings, the founder of the B.M.A.) is described, but, curiously, there is no particular mention of that of the university medical schools, which have played a considerable part in determining the future of medicine and will continue to do so. Despite that omission this is an admirable book.

A. P. THOMSON.

NEW LOOK FOR SAMSON WRIGHT

Samson Wright's Applied Physiology. Revised by Cyril A. Keele and Eric Neil. With the collaboration of John B. Jepson. Tenth edition. (Pp. 555+vii; illustrated. 60s.) London, New York, Toronto: Oxford University Press. 1961.

Samson Wright, professor of physiology in the University of London at the Middlesex Hospital Medical School, died in March, 1956. He was famous throughout the world as a gifted teacher and writer. The previous editions of his textbook had been translated into many languages—rightly so, since besides being a gifted exponent in the lecture theatre he possessed the power of writing. With this he presented with lucidity and pungency the points the student needed, but, in particular, more perhaps than any other one teacher he could "tear the guts" out of a new finding in the clinical field. He could show the physiological significance of the pathological point to the student of physiology and medicine but also enable the young physician and pathologist to know what was new in physiology, in its widest sense, and vital to him for his therapeutic advances.

The difficult task of replacing him and writing the tenth edition has been undertaken by his old pupil, Cyril Keele, for long his colleague as head of the department of pharmacology, and Eric Neil, his reader in physiology and later his successor in the John Astor chair in that school of medicine.

They have wisely approached this difficult task with boldness and courage and scrapped entirely the old format and transformed the book. The page size has been increased to 11 by 8½ inches with two columns to the page. They have entirely rewritten the section on circulation, respiration, muscle, nervous system, kidneys, and body water, and, most important, have inserted a new section on the two special senses, eye and ear. The elimination of footnotes and the inclusion of selected lists of reviews and important papers in groups within the chapters or at their end will make it much more readable. Though bigger it is in fact a more compact elucidation of specific points applicable to medicine. The authors are to be congratulated on the successful completion of their task: doubtless affection and regard spurred them to a successful issue.

A. ST. G. HUGGETT.

CHEMOTHERAPY OF CANCER

Biological Approaches to Cancer Chemotherapy. Edited by R. J. C. Harris. A Symposium held at Louvain, June, 1960, under the auspices of Unesco and the World Health Organization. (Pp. 431+x. 96s.) London, New York: Academic Press. 1961.

Since this book comprises the papers, and attendant discussion, given by 38 contributors to a symposium in June, 1960, the space allowed for this review does not permit mention of many distinguished contributions. The wide scope covered is indicated by descriptions of the role of hormones in normal and cancerous growth, the relation of viruses to cancer, electron-microscope studies of experimental tumour cells, biological alkylating agents, the mechanism of entry of drugs into cells, and immunological aspects of the control of tumour growth.

Papers by Talalay and by Furth, Mühlbach, and co-workers may be mentioned, because they throw light, respectively, on the biochemical relation between D.P.N. and T.P.N., and on the metabolism of steroid hormones;

and on the fascinating problems of how these hormones are concerned in the production of both hormone-dependent and independent (autonomous) tumours and in tumour inhibition and regression.

Excellent papers by Luria and Harris deal thoroughly with recent work on the virus-induced experimental cancers, but it is clear that these studies are still far from producing a rational approach to chemotherapy.

In the field of the bifunctional alkylating agents Bergel and co-workers describe a number of peptide derivatives of their "phenylalanine mustard." This was made in the D and L forms, of which only the latter (melphalan) was a tumour inhibitor; similarly the activity of the peptides seems to depend upon optical configuration, and it is hoped that eventually a peptide may selectively affect tumour tissue. Larionov, working in the same field, has found that the varying activity of the DL phenylalanine mustard (named sarcolysine) in different tumours is related to their different ability to take up phenylalanine and methionine into their protein content. Garattini and Palma report an admirably thorough investigation, with full statistical controls, of the inhibitory effects on the Walker tumour and various tissues of a number of alkylating agents and anti-metabolites. So far the tumour has usually shown less inhibition than normal tissues, but many other agents remain to be examined.

The development of 5-fluorouracil and some derivatives is described by Heidelberger, but the clinical results are rather disappointing. Maisin deals with the restorative effect of isologous bone-marrow and of ribonucleic acid on the bone-marrow of rats which has been damaged by alkylating agents; and with the clinical implications. In a stimulating paper on general cell theory and drug design Danielli discusses directions in which research could be rationally pursued. Some of the author's recent experiments are also described.

The book can be recommended to those seeking a broad and up-to-date survey of the subject defined by the title.

G. M. TIMMIS.

AMERICAN GERIATRICS

The Older Patient. By 21 Authors. Edited by Wingate M. Johnson, M.D. (Pp. 589+xiv; illustrated. $14.50.) New York: Paul B. Hoeber, Inc. 1961.

This book sets out to be a complete and practical guide to the diagnosis and treatment of the geriatric patient. It is an exceptionally well produced and illustrated volume, and for the most part is very readable. Many of its 21 authors are members of the staff of the school of medicine at Wake Forest College, Winston-Salem. Each is a specialist in his own branch of medicine or surgery, but it is doubtful if the majority are also specialists in dealing with geriatric patients.

The various comprehensive treatises on diseases of the elderly which have come out of the United States of America in the last 25 years seem to have aspired to be textbooks of general medicine also. It would be better if they were designed to be supplementary to rather than substitutes for the well-known American and English standard texts. Something more is to be expected from a book on clinical geriatrics than a discussion of the pathology, diagnosis, and treatment of the usual disorders of a system of the body, omitting mention of those which usually affect younger people. It is necessary to describe the natural history of diseases as they strike the older age group and where this differs from the expected, where the pitfalls in interpreting physical signs are, what prognostic signs are important, what modifications may be necessary in the programme of investigation and treatment, and why. In this sense a few sections of this book, and notably that on diseases of the nervous system, are particularly enlightening, but others betray the fact that they are based on an experience of middle age projected theoretically forwards. It is stated, for example, that pain occurs in myocardial infarction in all but 5% of cases, which is quite contrary to the experience of those who work principally with the elderly. Again, the two-step test is advocated for the electrocardiographic confirmation of angina pectoris, whereas in practice very few geriatric patients could even attempt it.

There are also some notable gaps. Physiotherapy for cases of stroke is dealt with in two sentences, and nothing is said of aids to daily living. The reader looks in vain for advice about the prevention and treatment of contractures and pressure sores, while little of practical use is said about the management of incontinence. Yet no one who has the handling of elderly patients can possibly ignore these mundane matters.

An attractive book which focuses attention on the older invalid must be welcomed, and this one contains much valuable information. Nevertheless it leaves the impression that modern ideas about the rehabilitation of disabled old people, which are the essence of geriatric medicine as practised on this side of the Atlantic, are outside its authors' experience.

J. N. AGATE.

VISUAL REFLEXES AND CEREBRAL FUNCTION

Les Réactions Opto-Motrices. Contribution à l'Étude des Fonctions du Cerveau. By H. W. Stenvers. Preface by R. Garcin. (Pp. 133+vii; illustrated. 26 NF.) Paris: Masson et Cie. 1961.

This short and unusually interesting monograph deals with three reflex reactions involving vision in so far as it concerns cerebral functions. The first is the well-known opto-kinetic nystagmus, the diagnostic importance of which in diseases of the brain was first pointed out by Bárány in 1930 when he stressed the failure of "train-nystagmus" to develop when the stimulation derived from the hemianopic side. The normal reflex with its slow and rapid phases is well known: the first a following of an object moving in the visual field, and the second a return to fixation excited by the appearance of another object appearing in the field. The author produces evidence that the slow phase depends on the integrity of the angular gyrus of the contralateral side; the rapid phase depends upon the fixation reflex.

In addition to the normal reflex, however, he describes a second and somewhat similar mechanism dependent on conditional reflexes, in which the rapid phase depends on the ocular areas of the contralateral frontal lobe and the slow phase on the homolateral. It remains functional in pathological cases when the cerebrum is unaffected but the retino-cortical pathway to one hemisphere is unilaterally interrupted by a lesion in the optic tract; nor is it eliminated on the affected side by a hemianopia. Its extinction towards one side must be considered a symptom of grave cerebral damage. The blinking reflex in response to a menacing gesture is found to be an elementary function of the occipital and frontal lobes; while the ability to localize objects visually in the peripheral field is dependent on the activity of the medial aspects of the occipital lobes and

the posterior part of the corpus callosum, each occipital lobe concerning itself with the contralateral visual field.

The monograph contains several new ideas and is illustrated with elaborately studied clinical cases. It is of more than usual interest both to the neurologist and to the ophthalmologist.

STEWART DUKE-ELDER.

INTERNATIONAL GOITRE CONFERENCE

Advances in Thyroid Research. Transactions of the Fourth International Goitre Conference, London, July, 1960. General Editor: Rosalind Pitt-Rivers. (Pp. 537+xxvii; illustrated. £6 6s.) Oxford, London, New York, Paris: Symposium Publications Division, Pergamon Press. 1961.

Though diverse views may be held about the desirability of publishing original material in the form of conference reports instead of in the regular periodicals it appears that the practice (which received so much impetus during the second world war) has come to stay. Its great advantage to the reader is that it collects into one convenient volume a great deal of up-to-date research in a given field; this is outstandingly true of the present volume.

Lest the price of this book be considered high it should be borne in mind that it is now 22 years since the last international goitre conference and that the present report contains 95 papers on a very wide range of subjects of interest in thyroid research. Though some of these are technical or biochemical in emphasis many will have a direct clinical appeal. Examples of such papers—to pick a few at random—are those on "Myocardial Infarction in Thyrotoxicosis," "The Differential Diagnosis of Thyrotoxic Myopathy and Myasthenia Gravis," "The Value of the Ankle Jerk in Diagnosing Hypothyroidism," "Tracheal Stenosis following Thyroidectomy," and "The Occurrence of Leukaemia Following Radioiodine Therapy."

The majority are more technical in content and will appeal especially to those interested in the growing front of knowledge in thyroid research. Many deal with the intermediate metabolism of the thyroid in animals as well as in human disease. Nearly all the papers are commendably brief and concise in presentation, and the great majority are also provided with a generous list of recent and well-chosen references.

In his introductory remarks Sir Charles Harington appeals for a critical refusal to accept the facile explanation of results. In such a context it is a pity therefore that no reports are included of the discussion of any of these papers, for this surely was one main purpose of the conference. But to include them would have increased not only the bulk but also no doubt the price of the book. The volume is very well produced with clear type and on good paper. It will prove an essential reference volume for all engaged in thyroid research, and clinicians who are not engaged in research will also find in its pages a great deal of lively clinical interest.

C. L. COPE.

MYASTHENIA GRAVIS

Thymectomy for Myasthenia Gravis. A Record of Experiences at the Massachusetts General Hospital. By Henry R. Viets, M.D., and Robert S. Schwab, M.D. (Pp. 143+xv; illustrated. 56s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The authors of this short monograph, writing from the Myasthenia Gravis Clinic of the Massachusetts General Hospital, have an extensive experience of the disease, as they have treated some 500 cases since 1935. The main purpose of the book is to evaluate the results of thymectomy—which has been performed in 139 of their patients, 26 of them having thymomas—and to compare these results as objectively as possible with those obtained in patients of similar age and sex and with similar duration and severity of disease who have been treated medically. They consider that in women under 40, in whom the disease is moderate to severe, thymectomy is of undoubted value in precipitating a remission; in men the conclusions are less certain, but there are some indications that it is of value. When there is radiological evidence of a thymoma the authors agree with Keynes that irradiation is the right treatment in the first instance, usually followed by removal of the tumour and thymus. There are good discussions by Dr. Sweet and Dr. Vanderveen of the technique of the operation and of the anaesthetic problems involved. The authors emphasize the importance of the post-operative management, but, strangely, do not mention the importance of breathing exercises and physiotherapy for the chest, which are of major value. They are possibly unduly worried about the danger of a cholinergic crisis due to over-dosage in the post-operative period. The monograph also contains a short account of the clinical features of the disease, an excellent concise account of the thymic pathology by Dr. Castleman, an account of the radiology by Dr. Robbins, and an admirable historical introduction by the senior author. It is particularly fitting that this excellent book is dedicated to Dr. Mary Walker and Dr. Blalock, the pioneers in the medical and surgical management of this disease.

J. W. ALDREN TURNER.

CONTROVERSIAL BORDERLAND

Ciba Foundation Study Group No. 6. *Metabolic Effects of Adrenal Hormones in Honour of Professor G. W. Thorn.* Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor. (Pp. 109+viii; illustrated. 12s. 6d.) London: J. and A. Churchill Ltd. 1960.

This small volume contains a detailed account of a recent Ciba Foundation Study Group meeting which was held in honour of Professor G. W. Thorn. The topics discussed and the opening speakers were "Actions of Cortisol and Related Compounds on Carbohydrate and Protein Metabolism" (C. N. H. Long, O. K. Smith, and E. G. Fry); "The Role of Adrenal Steroids in the Regulation of Hepatic Metabolism" (J. Ashmore); "The Adrenal Gland and *in vitro* Protein Synthesis" (A. Korner); "Action of Cortisol on Trapping of Amino Acids by the Liver" (H. N. Christensen); "Effect of Adrenal Hormones upon Adipose Tissue" (A. E. Renold, G. F. Cahill, Jr., B. Leboeuf, and M. G. Herrera).

The symposium and this account of it are a fitting tribute to a distinguished research worker in the field of adrenal physiology. The original papers contain a wealth of information and the detailed reports of the subsequent discussions add greatly to the value of the book. Investigators who are interested in the metabolic effects of the adrenocortical hormones will certainly wish to have this book in their libraries. It can also be recommended to other biochemically inclined readers who wish to have a readable and critical account of some of the recent fundamental work in a controversial borderland between biochemistry and endocrinology.

R. W. E. WATTS.

TRANSPORT OF IONS

Transport and Accumulation in Biological Systems. By E. J. Harris, Ph.D., D.I.C., D.Sc. Second edition. (Pp. 279+xi; illustrated. 50s.) London: Butterworths Scientific Publications. 1960.

This is essentially a revised edition in which developments taking place during the past four years have been incorporated. (It is described as "a revised and enlarged edition" but actually contains 279 pages as against 291 in the first edition.) Written by a biophysicist who has been in the forefront of research on the transport of ions in several biological systems and who has a thorough understanding of the physico-chemical principles concerned in the movements of ions and molecules, this book is unquestionably of considerable value to all who are carrying out research in such problems as urinary secretion, absorption from the intestine, gastric secretion, haemolysis, and so on.

My only criticism is that the author has covered a very wide field in a very small compass, with the result that the writing is almost telegraphic in style to the great prejudice of its intelligibility to those not so familiar as he is with the topics discussed. I feel that if more space had been taken or if the scope had been limited the book would have a much wider appeal.

HUGH DAVSON.

HOME TREATMENT

Home Treatment in Injury and Osteoarthritis. By W. E. Tucker, C.V.O., M.B.E., T.D., M.A., M.B., B.Ch., F.R.C.S. With a foreword by Sir Harry Platt, Bt., LL.D., M.D., M.S., F.R.C.S. (Pp. 80+viii; illustrated. 10s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1961.

Advice to patients that they should purchase and read "my book" has rather gone out of fashion since John Abernethy's day. This is a pity, particularly when the advice might be given by a man who practises what he preaches. Such is the case with Mr. Tucker, whose book should be recommended to every bookseller with whom orthopaedic surgeons and rheumatologists have contact. It is illustrated by simple line drawings and contains much sound advice, including groups of worthwhile remedial exercises. The chapter on slimming is a little too vague (what, incidentally, is "devitalized sugar"?); it would be improved by a few itemized specimen diets with some indication of their calorie contents.

Why don't hospital out-patient departments have book stalls on which a selection of books like this might be sold—with, of course, *Family Doctor*?

NORMAN CAPENER.

As a result of two long sea voyages, Sir A. Bradford Hill tells us in the seventh edition of his *Principles of Medical Statistics*, he has made considerable changes to the text. And, as often happens after long sea voyages, the book has put on a bit of weight. It remains, nevertheless, the best introduction to its subject that a medical man can have, a uniquely clear, concise, and pertinent exposition of statistical ideas and techniques. New chapters are concerned with sampling and with measurements of sickness, while other additions to the text cover the "t" test and procedures in carrying out clinical trials. The lone reader teaching himself from this book will find near the end some realistic problems on which to test his knowledge, and (unlike in life) the answers a few pages later. The book is published by The Lancet Ltd. (pp. ix+367; 12s. 6d.).

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

A New System of Anatomy. By Sir Solly Zuckerman, C.B., M.A., M.D., D.Sc., F.R.S. (Pp. 579+xiii; illustrated. 75s.) London, New York, and Toronto: Oxford University Press. 1961.

Neoplastic Disease at Various Sites. Volume 4: Tumours of the Oesophagus. By Norman C. Tanner, M.D., F.R.C.S., and D. W. Smithers, M.D., F.R.C.P., F.F.R. (Pp. 352+xi; illustrated. 63s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Diagnostik der Neuroendokrinen Krankheiten und Ihre Pathophysiologischen Grundlagen. By Professor M. Julesz and Dr. I. Hollo. (Pp. 857; illustrated. No price.) Budapest: Akademiai Kiado. 1961.

The Coil of Life. By Ruth Moore. (Pp. 418+xv; illustrated. 40s.) London: Constable. 1961.

Williams' Obstetrics. By Nicholson J. Eastman and Louis M. Hellman. 12th edition. (Pp. 1,230+x; illustrated. $16.) New York: Appleton-Century-Crofts, Inc. 1961.

Papers Presented at a Residential Refresher Course held by the Association of Psychiatric Social Workers, Oxford, 1961. By Elizabeth E. Irvine. (Pp. 100+viii. 10s.) London: Association of Psychiatric Social Workers. 1961.

Outline of Orthopaedics. By John Crawford Adams. Fourth edition. (Pp. 448+vii; illustrated. 35s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Poliomielita. By St. S. Nicolau, Al. Radulescu, N. M. Constantinescu, N. Cajal, and G. Marinescu. (Pp. 771; illustrated. No price.) Bucuresti: Academiei Republicii Populare Romine. 1961.

Probleme de Chirurgie Experimentala Vasculara si Cardiaca. By Tiberiu Ghitescu. (Pp. 375; illustrated. No price.) Bucuresti: Academiei Republicii Populare. 1961.

Patterns of Hospital Ownership and Control. By James A. Hamilton, with the assistance of R. Bruce Butters, M.H.A., and Elbert E. Gilbertson, M.H.A. (Pp. 166+vii; 36s.) Minneapolis: University of Minnesota Press. 1961.

La Maladie de Quinck. By Pierre Blamoutier. (Pp. 106. No price.) Paris: Expansion Scientifique Française. 1961.

The Myocardium—Its Biochemistry and Biophysics. By Alfred P. Fishman, M.D. (Pp. 542; illustrated. No price.) New York: American Heart Association and New York Heart Association. 1961.

The Life Savers. By Ritchie Calder. (Pp. 191. 2s. 6d.) London: Pan Books Ltd. 1961.

Frustration. The Study of Behavior Without a Goal. By Norman R. F. Maier. (Pp. 264; illustrated. No price.) The University of Michigan Press. 1961.

Blacklock and Southwell: a Guide to Human Parasitology for Medical Practitioners. By T. H. Davey, O.B.E., M.D. (Belf.), D.T.M.(Liver.). Seventh edition. (Pp. 223+viii; illustrated. 30s.) London: H. K. Lewis and Co. Ltd. 1961.

Les Ostéo-arthropathies Nerveuses. By A. M. Recordier, P. Mouren, and G. Serratrice. (Pp. 167; illustrated. No price.) Paris: Expansion Scientifique Française. 1961.

Vertebral and Carotid Angiograms in Tentorial Herniations. By Hans F. Plaut, M.D. (Pp. 155+xvii; illustrated. 84s.) Springfield, Illinois: Charles C. Thomas. 1961.

The Image. Knowledge in Life and Society. By Kenneth E. Boulding. (Pp. 175; 10s. 6d.) University of Michigan Press. London: Cresset Press. 1961.

A Handbook on Hanging. By Charles Duff. (Pp. 191. 15s.) London: Putnam and Co. Ltd. 1961.

A Student's Guide to Anatomy. By David Sinclair, M.A., M.D. (Pp. 91; illustrated. 7s. 6d.) Oxford: Blackwell Scientific Publications. 1961.

Medico-Legal Forms with Legal Analysis. By Law Department American Medical Association. (Pp. 49; No price.) Illinois: American Medical Association. 1961.

Camera Close Up. By O. R. Croy. (Pp. 240; illustrated. 37s. 6d.) London and New York: The Focal Press. 1961.

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"A PRETTY GHASTLY, AWFUL PICTURE"

A succession of Ministers of Health and their advisers have been so immersed in the routine of their jobs, or so busy explaining to visitors what a marvellous thing the N.H.S. is, that they and their staffs and the numerous administrators in the Health Service have concealed from each other and the public that medicine in Britain is in a mess. Last week Lord Taylor, opening a debate in the House of Lords on the growing shortage of doctors, described, in a place not encouraging exaggeration, the present position as "a pretty ghastly, awful picture," and as "a new and desperate situation." It is difficult to believe that everyone all the time has been unaware of what was happening, yet the recent disclosures in these columns[1] and elsewhere, that, outside the teaching hospitals, the N.H.S. hospitals to a great extent depend for the continuation of their work upon some 4,000 foreign doctors, a large proportion from India and Pakistan, have caused surprise. They do not, of course, come here in order to prevent the N.H.S. hospitals from coming to a standstill, but in order to gain experience and often enough to earn a better living than at home. Both of these are excellent reasons for emigrating from one country to another, and as they come in here we see leaving Britain for other countries British-born doctors with British qualifications. Welcome though the advent of foreign doctors is, we share the view of a prominent Ministry of Health spokesman[2] that the way they gain experience is the best neither for themselves nor for the British patients who provide them with it. Lord Taylor has backed up by his own inquiry the evidence published in the *Journal* of what is happening in the region of the Sheffield Hospital Board. He found, for example, such a state of affairs in mental hospitals as to conclude: "it is very rare indeed that you will find the staff of a mental hospital now is an English or a British staff." There also appears to be a shortage of casualty officers. Referring to the non-teaching hospitals—by far the largest number in the N.H.S.—he said:

> "I cannot recommend your Lordships to go into such hospitals as a casualty, for there is in many cases no casualty officer. A house-surgeon will have to leave the theatre when he can, to treat you, and his experience will be far less than that of your own general practitioner. When he comes he will probably not be a British graduate and he could well have difficulty in understanding what you say. This is at a time when speed and efficiency may be literally life saving."

Professors F. Lafitte and J. R. Squire published a paper last year[3] which questioned the findings of the Willink Committee. The Committee underestimated the rate of growth of the population and also the number of doctors needed. It recommended a cut of 10% in the intake of medical students from 1961. As Lord Cohen, in a spirited and subtle defence of the Willink Report in the Lords debate, pointed out, the Committee recognized that many of their assumptions, estimates, and calculations, were speculative. If they were indeed so speculative, then it just shows how in these days everyone can be bemused into acceptance and inaction as a result of the findings of one of these high-powered governmental committees which seem to be symptomatic of the static society which is Britain to-day. But as Dr. J. R. Seale observes in an article elsewhere in this week's *Journal* (p. 1554) there had been a substantial reduction in the intake of medical schools before the publication of the report. Even if it can have had little effect on the present shortage of doctors it has certainly had its effect upon the way people have been thinking about the Health Service. The majority of the Royal Commission on doctors' pay, for example, thought that recruitment was not a factor to which they need "attach special weight" in making recommendations on current pay. What an incredible state of affairs!

It was only Professor John Jewkes in his Memorandum of Dissent who saw things as they were and not as others wished them to be. He gave a table which suggested that, to quote his words, "perhaps the supply of doctors is not nearly so secure as it might then have appeared." The table showed that the number of full-time medical students entering universities for the first time fell between 1955 and 1958 by about 9%, and that the total full-time medical student population had shown an almost continuous decline since 1950–1. He noted, too, the increase in the number of foreign medical students in British universities. Professor Jewkes drew attention to the fact that between 1939 and 1958 the increase in full-time university students in Arts was 70%, in Science 183%, in Technology 162%, in Dentistry 93%, in Veterinary Science 356%—and in medical students 7%. "It may be

[1] *Brit. med. J.*, October 7, 1961, p. 950.
[2] See leading article, *Brit. med. J.*, 1961, 2, 572.
[3] *Lancet*, 1960, 2, 538.
[4] *Brit. med. J.*, 1957, 2, 1166.

permissible to wonder why," he wrote, "an increase of 7% in medical students in this period is thought adequate, even in an epoch when the demand for medical services and the claims of medical research have so much increased." Professor Jewkes realized how difficult it was to say how quickly the rate of entry into medicine would be influenced by changes in the level of earnings of other professions. Some time lag must be taken for granted. Once a trend was established it might well possess great momentum. In his view it "would be imprudent to be over-confident about the continued supply of doctors." Professor Jewkes's conclusion was published seven months before the conclusions of the Willink Committee were criticized by Lafitte and Squire. It is being stated that everyone accepted the conclusions of the Willink Committee, but in an annotation on the forecast being made at the end of 1957 about the Willink Committee's report we observed this[4]: "If it is true that the Willink Committee is advocating a numerical limit on the entry of medical students on the basis of predicting something which is almost unpredictable—that is, the future medical needs of this country—one possible explanation would be that such a recommendation is related not so much to medical needs as to the cost of the Service." Certainly the Pilkington Commission subsequently found the Willink Report helpful to it in framing its proposals for paying doctors in the Health Service.

Lord Cohen concluded his gallant defence of the Willink Report by saying: "The crux of the matter is: are there sufficient doctors?" And the answer he gave was, No. The figures given in Dr. J. R. Seale's paper elsewhere in this issue back this up. Moreover Seale suggests that if the exodus of young British doctors continues then the now recommended 10% increase in the intake of medical students will still not make good the wastage from this cause after 1968. And Seale is bold enough to say this: "Young British doctors will remain in the N.H.S. only if conditions of service are reasonably attractive. By their actions rather than by their words they have shown that they are unattractive." We therefore beg leave to doubt the value of the numerous remedies, apparently all sound enough on paper, made by Lord Taylor and other speakers in the debate, reported in our parliamentary columns. Lord Beveridge, we believe, went to the root of the matter when he told his fellow Peers of the conclusion of a recent conference of experts "that there should be an inquiry, not simply as to how much doctors and surgeons and dentists should be paid and from what sources, but into how the Health Service of the State should be organized in practice and *how it should be related to voluntary provision for health made by the citizens themselves.*" (Our italics.) Referring to the suggestions being made about opting out of the Health Service, Lord Beveridge said he thought that this was worth inquiring into "so that we may keep welfare in this country, with all the necessary action that the State alone can take, taken by it, with *room left for action by the individual for himself.*" (Our italics.)

It is obviously time that Britain stopped the kind of self-praise that has been really no recommendation for its National Health Service. Whilst no one would lay the whole cause of our present discontents at its door, it would be unwise to exculpate it. As Dr. Seale says, it is better to look at what people are doing, and the fact that doctors are emigrating in the numbers that are known, and that a few general practitioners are giving up the financial security of practice in the N.H.S. for the hazards of private practice, should at least remind us that everything is not for the best in the best of all possible worlds. We hope that the report of the Porritt Committee will throw some light into dark places.

SUPPRESSION OF COUGH

Cough is a protective physiological reflex which is present in health as well as in disease. Its purpose is to keep the respiratory tract free from particulate matter and accumulated secretions. The usual stimuli which initiate the act of coughing are noxious agents, infective, chemical, or mechanical, irritating some part of the mucous membrane of the respiratory tract, but the reflex can also be elicited from other receptor areas such as the gastric mucosa. Although it is a reflex action coughing can be voluntarily suppressed and conversely may be centrally originated.

Since coughing is a protective reflex every attempt must be made to identify the cause and if possible remove it. This entails a full assessment of the case and in particular of the circumstances in which coughing occurs. When this is done some simple remedy may emerge which will solve the problem. The cessation of smoking is an obvious example. The chronic bronchitic who starts to cough at night as soon as he retires to bed may do so because he moves from a warm sitting-room to a cold bedroom; the installation of a convector type of radiator in the bedroom may be more effective than any medication. In the majority of cases of troublesome cough there

is some disease of the respiratory tract and treatment in the first instance should always be directed to it. The chronic bronchitic who is coughing to get rid of purulent sputum may be relieved of his cough by a course of postural coughing and the administration of an antibiotic to eliminate the infection. Only after these aspects have been fully considered and dealt with as far as possible should the use of drugs to suppress the patient's cough be considered.

The majority of drugs that suppress cough act centrally on the cough centre and have a general narcotic action in addition to their antitussive effects. The oldest of them are opium and its derivatives. Preparations such as camphorated opium compound mixture (*B.N.F.*), codeine linctus (*B.P.C.*, *B.N.F.*), syrup of codeine phosphate (*B.P.C.*), and linctus of diamorphine (*B.P.C.*) are still widely used, for there is little evidence that any of the newer drugs are greatly superior to these well-tried remedies. Codeine is probably the drug most often prescribed to suppress cough. It is preferred to morphine because it does not depress respiration so much, because side-effects such as nausea, vomiting, and constipation are less common, and because addiction, though it may occur, is relatively rare. Syrup of codeine phosphate is commonly used, but the drug is equally effective in tablet form. (Owing to an unfortunate slip, later corrected by several correspondents, codeine linctus, which contains syrup of codeine phosphate, was wrongly described in these columns recently as almost useless.[1]) Opinions vary on the dosage to be prescribed for chronic cough. Some consider that a large dose of 60 mg. of codeine phosphate should be given three or four times daily,[2] whereas others advocate a dose of 15 mg. or 4 ml. of the syrup of codeine phosphate every two hours.[3] Dihydrocodeine (" D.F. 118 ") is pharmacologically more active than codeine and has fewer side-effects, but the danger of addiction is greater. In the treatment of chronic cough a long-acting preparation in which dihydrocodeine and the antihistamine phenyltoxolamine are combined in a sulphonic resin complex has recently received favourable reports.[4 5] Many physicians believe that the best drug in cases of pulmonary neoplasm and other inevitably fatal conditions accompanied by painful or distressing cough is diamorphine hydrochloride (heroin) and it is mainly for this purpose that the drug is still prescribed in Great Britain. The usual dose is 6 mg. and it is usually better to give it orally as 8 ml. of the linctus of diamorphine than as a hypodermic injection. The danger of addiction is great, however, and unless it is certain that the patient's expectation of life is short some other drug should be preferred.

Of newer cough suppressants of the narcotic type probably the best is pholcodine. It has been shown to be rather more effective than codeine[2] and as effective as diamorphine.[6] It has few toxic effects, and since it does not cause euphoria addiction is uncommon. The dose is 10–15 mg. in the form of a linctus or flavoured syrup, and many proprietary cough mixtures now contain pholcodine as the main active ingredient. Methadone is another narcotic cough suppressant; its antitussive effect is similar to that of diamorphine and it is also an analgesic, but it depresses respiration and therefore should be used with caution for many respiratory diseases, especially in children. It is a drug of addiction and should be given for brief periods only. The dose is 2–5 mg. given either as methadone linctus (*B.N.F.*) or in tablet form.

It is generally thought that these drugs suppress cough by a central action on the cough centre. Work by H. K. Beecher,[7] however, has cast doubt on this belief. He found both with experimentally induced and pathological cough in man that neither codeine nor diamorphine significantly reduced the actual frequency of coughing, and he suggests that the beneficial effect of these drugs in patients with chronic cough may be due to their euphorigenic or hypnotic properties rather than to any specific antitussive activity.

A number of centrally acting non-narcotic cough suppressants are now available. These include dextromethorphan (" romilar "), carbetapentane (" toclase "), oxeladin (" pectamol "), sodium dibunate (" becantyl "), piperidione (" sedulon "), and caramiphen (" taoryl "). In general these are less potent than the drugs mentioned above, but because they are not narcotics and do not cause addiction they are more suitable for long-term use. A recent addition to this group is pipazethate (" selvigon "). In a clinical trial recently reported in this journal[8] it was shown to have an antitussive effect similar to that of codeine and to have fewer side-effects.

Cough may also be suppressed by substances which act peripherally and inhibit the stimulus which initiates the cough reflex. Simple remedies of this nature are local analgesic and demulcent tablets or lozenges, which may be sucked by patients with tonsillitis or pharyngitis, and inhalations of various kinds which liquefy tenacious sputum and enable it to be coughed up readily so that the patient clears his respiratory tract and then has a period of freedom from coughing. Benzonatate (" tessalon ") is a peripherally acting cough suppressant which has a selective action on the pulmonary stretch receptors; it is particularly valuable when chronic cough is

[1] *Brit. med. J.* 1961, 2, 1004.
[2] Aistead, S., *Dilling's Clinical Pharmacology*, 20th ed., p. 336. London. 1960.
[3] Bickerman, H. A., in *Drugs of Choice 1960-61*, ed. Modell, p. 493. St. Louis. 1960
[4] Townsend, E. H., *New Engl. J. Med.*, 1958, **258**, 63.
[5] Cass, L. J., and Frederik, W. S., *Ann. Intern. Med.*, 1958, **49**, 151.
[6] Snell, E. S., and Armitage, P., *Lancet*, 1957, **1**, 860.
[7] Beecher, H. K., *Measurement of Subjective Responses*, p. 399. Oxford University Press. 1959.
[8] Prime, F. J., *Brit. med J.*, 1961, **1**, 1149.
[9] Illingworth, R. S., ibid., 1960, **1**, 873.

associated with bronchospasm. The dose is 100 mg. thrice daily over a period of two weeks; there is often a latent period of two to four days before the drug is effective and the maximum effect is usually obtained five to seven days after the start of treatment. Side-effects are rare.[3]

Cough in children is nearly always productive and should seldom be suppressed; treatment of the cause is the first essential. If some form of cough mixture is required R. S. Illingworth[9] recommends either the simple linctus for infants *B.P.C.* or opiate linctus of squill for infants—the dose of each being 3.5 ml.—or for a dry irritating cough the codeine mixture for infants *B.P.C.* Finally there is the patient who has a chronic, irritating, dry cough but no other manifestations of respiratory disease. The cough then is usually a nervous tic of psychogenic origin, and as with other psychosomatic symptoms treatment is more likely to be effective if it is directed to the underlying factors rather than to a pharmacological attack of the presenting feature.

TRENDS IN CHILD PSYCHIATRY

In 1909 Dr. William Healy established a "behaviour clinic" to serve the Chicago Juvenile Court. In it, and under his medical direction, he drew together the social, psychological, and medical approaches. Evolving directly from this clinic, and with the backing of the Commonwealth Fund, eight demonstration clinics under the name of "child guidance clinics" were set up, soon to be copied in London and other European capitals. Spurning delinquency, some of the clinics became centred on schools, sometimes under the direction of an educational psychologist. By 1939 the Feversham Report, reviewing the voluntary mental health services, recommended two types of clinic, one centred on the school service the other on the health service, and this was confirmed in the Education Act of 1944 and in C. P. Blacker's report[1] in 1946.

With the coming of the National Health Service the Ministers of Education and Health and the Department of Health for Scotland in their respective circulars[2] perpetuated a blurring of the functions of these two types of clinic, envisaging the supply by regional hospital boards of psychiatrists to work in education-authority clinics. In 1948 the National Association for Mental Health and the British Paediatric Association jointly expressed their concern at these arrangements, which in some areas meant that "a psychologist without medical qualifications can be entrusted with the ascertainment and in some cases even the diagnosis and treatment of disorders in childhood which, in many instances, call for much more general handling." The report of the Minister of Education's Committee on Maladjusted Children[3] and subsequent circulars[4] have not eased the situation, despite clear advice from the Council of the British Medical Association.[5] Several further authoritative criticisms have been made and have demonstrated that this is not a matter of striving for power or of "empire building" but of concern for the child. G. R. Hargreaves[6] in 1958 wrote, "The educational clinic is completely detached from the medical and biological sciences, and its relationship to the social sciences is largely restricted to educational theory and education psychology." The Royal Medico-Psychological Association enumerated its criticisms[7] of the *Report on Maladjusted Children*, and the Psychological Medicine Group of the B.M.A. deprecated "the perpetuation of the bias towards the educational aspects of the problem and the failure to emphasize the importance of relating child psychiatry to the general body of psychological medicine.[8] Also relevant is the Ingleby Committee's[9] insistence on a clear distinction between ascertainment of problems, accurate diagnosis and treatment, and co-ordination of resources.

Now the Association of Teachers of Psychiatry in Undergraduate Medical Schools, through their spokesmen Professor Desmond Curran and Dr. Gerald Garmany,[10] make a vigorous appeal to abandon the term child guidance, and for the Minister of Health to assume full responsibility for the alternative "child psychiatry" (they evidently do not favour a recent plea[11] for a further alternative term—"family psychiatry"). They also urge that the paediatric hospital or department is the ideal site for the child psychiatric clinic; in so doing they might have added the argument that the recruitment of child psychiatrists would thus be encouraged through participation in undergraduate training, as expounded by Dr. Mildred Creak.[12]

It may be argued some child psychiatrists in clinics away from hospitals find no difficulty whatever in obtaining adequate hospital investigations and in keeping in touch with their medical colleagues. Paediatric hospitals tend to be regional, whereas child psychiatric clinics should be more widespread. Again, criticism of the London Care Committees fails to take into account the fact that the Care Committee workers attend at the periodical school medical inspections, and general practitioners are sometimes invited to their case conferences. There are still children whom the Care Committee can help but who otherwise

1 Blacker, C. P., *Neurosis and the Mental Health Services*, 1946, London.
2 Circular 179, R.H.B. (47) 13; R.H.B. (1) (48) 9.
3 *Report of the Committee on Maladjusted Children*, 1955, H.M.S.O., London.
4 National Health Service—Child Guidance, H.M. (59) 23; Ministry of Education circular 347.
5 Annual Report of Council, *Brit. med. J. Suppl.*, 1958, 1, 170.
6 Hargreaves, G. R., *Psychiatry and Public Health*, 1958, London.
7 Royal Medico-Psychological Association, Memorandum on the "Report of the Committee on Maladjusted Children."
8 See leading article, *Brit. med. J.*, 1959, 2, 1391.
9 Home Office, *Report of the Committee on Children and Young Persons*, 1960, H.M.S.O., London.
10 Curran, D., and Garmany, G., *Brit. med. J.*, 1961, 2, 1500.
11 *Brit. med. J. Suppl.*, 1961, 1, 60.
12 Creak, Mildred, *Lancet*, 1959, 11, 481.

would be left neglected. So members of the child psychiatric team will not be solely concerned with clinical, administrative, and teaching duties: co-operation with numerous other agencies, including education authorities, will still be essential.

MATERNITY BEDS IN LONDON

In the London County Council's area 83% of the babies born in 1960 were born in hospital.[1] The Cranbrook Committee[2] recommended a figure of 70% as a national average. Londoners may therefore be inclined to congratulate themselves on being so well provided with maternity beds—a total of 2,153 in teaching and non-teaching hospitals. But there is another side to the picture. The number of women in labour for whom a maternity bed has to be found by the Emergency Bed Service has been rising fast: in 1958 it was 1,125 and in 1960 it was 1,767 (these figures are for the County of London only). In his annual report[1] for 1960 Dr. J. A. Scott, county medical officer of London, explains why it is becoming increasingly difficult for general practitioners or the council's antenatal clinics to book a maternity bed for a mother on grounds of age, parity, or social conditions if the woman attends for antenatal care for the first time during the second half of pregnancy. In general what happens is that the beds which such women might occupy have already been allotted (not necessarily because of obstetric or social need) to mothers who attend the hospital antenatal clinics in the early weeks of pregnancy.

The London Local Medical Committee has co-operated in a scheme to help women enter hospital who despite their need cannot obtain a hospital booking. The general practitioner undertakes the antenatal care of these women, visits them when labour begins, and then obtains a bed through the Emergency Bed Service. He is paid a "partial" maternity fee for his services. Alternatively, if no general-practitioner obstetrician can be found to give this care, one of the council's midwives follows the same procedure.

Dr. W. G. Harding, a divisional medical officer for North-west London, has examined the records of 100 women admitted to a maternity bed through the Emergency Bed Service.[1] The cases were successive. Twenty-four had no antenatal care before they went into labour, 28 had been looked after by general practitioners, and 48 had attended the Council's antenatal clinics. In only 14 cases did complications arise which rendered a previously booked home confinement undesirable. In the remaining 86 cases the Emergency Bed Service was used in order to secure hospital beds because of unsuitable home conditions. Dr. Harding records that 23 of these women had moved into the area less than six weeks before their expected date of confinement, but he adds that there is evidence to show that an increasing number of other women fail to present themselves for antenatal care in good time because they think they stand a better chance of getting a bed if it is arranged at the last moment through the Emergency Bed Service.

Not surprisingly the Emergency Bed Service, while emphasizing that it is happy to deal with genuine obstetric emergencies, deplores the situation which has arisen. The Emergency Bed Service deals with a larger area than that of the L.C.C., and in the year 1960–1 it arranged the admission to hospital beds of 3,263 women in labour, compared with 2,693 in the previous year.[3] As many as 52% of these women had attended a general practitioner or antenatal clinic, and it was known well beforehand that hospital confinement would be necessary for them on social grounds. "It seems absurd," the report of the Emergency Bed Service remarks, "that in so many cases it should prove impossible to book a bed for these patients in advance and that they should in consequence have to be admitted as 'emergencies' after labour has started."

[1] London County Council, *Report of the County Medical Officer of Health and Principal School Medical Officer for the Year 1960*, County Hall, London S.E 1.
[2] Ministry of Health, *Report of the Maternity Services Committee, 1959*, H.M.S.O., London.
[3] King Edward's Hospital Fund for London, *Emergency Bed Service. Report for the Year Ended 31st March, 1961.*

AGRICULTURAL PESTICIDES

The application of pesticides to growing and to stored crops has enabled much greater yields to be obtained than formerly. But most pesticides are toxic to organisms other than those they are specifically intended to destroy. They may be harmful to the person who applies them, to the consumer of food derived from the crop, or to wild animals and plants accidentally contaminated.

A Government report[1] issued this week considers that the hazard to users of pesticides is "minimal if the regulations laid down or recommendations made are properly observed." Since regulations to control their use came into operation in 1953 few non-fatal accidents on farms have been attributed to pesticides and only one death has been reported. Even so, trade union representatives told the committee that they considered more should be done to enforce the regulations and that the inspectorate should be enlarged. As to the consumer of foodstuffs, the committee received no evidence of harm to anyone. But it recommends that "further selective survey work should be undertaken to determine pesticide residues in food, both home produced and imported." Damage to wild life[2] is admitted to have been considerable, and the committee calls for more research into the organisms affected and the poisons which are particularly hazardous to them. The report ends by recommending that additional staff should be appointed to study and control the use of pesticides. While the growing number and variety of these substances clearly makes that necessary, it is worth emphasizing, as was done recently in these columns,[3] that more medical men should be appointed to investigate possible risks to health.

[1] *Toxic Chemicals in Agriculture and Food Storage.* Report of the Research Study Group on Toxic Chemicals in Agriculture and Food Storage to the Minister of Agriculture, Fisheries and Food, the Minister for Science, the Secretary of State for Scotland, and the Minister of Health, 1961. H.M S.O., London. 4s. 6d.
[2] *Brit. med. J.*, 1961, **1**, 651.
[3] Ibid., 1961, **2**, 1411.

LONDON'S LOCAL GOVERNMENT

The report[1] of the Royal Commission on Greater London which appeared a year ago has stimulated the Government to an unusually quick response, particularly since many of the recommendations were controversial and provoked immediate opposition. A White Paper issued last week stated that "the Government's main conclusion is that the Commission were justified in their criticism of the present structure of local government in Greater London, and that their broad design should be adopted as the basis for improving it." In brief, the broad design was that an upper and lower tier of authorities should be replaced by the conception of the Greater London borough as the primary unit of local Government performing its functions (including public health, welfare, and children's services) within its own limited area, and that there should be a directly elected Council for Greater London as a unit of local government performing functions for which a large area is essential, such as traffic control, town planning, fire and ambulance services, and refuse disposal (but not collection). These proposals would mean the abolition of the administrative counties of London and Middlesex, the loss to the counties of Essex, Hertfordshire, Kent, and Surrey of the metropolitan parts of their areas, and removal of county borough status from Croydon, East Ham, and West Ham.

The area of Greater London concerned in this change has a population of nearly 9 million, and local government is now carried on by about 100 borough and urban district councils. It is a serious defect, the White Paper remarks, "that many of the boroughs, especially the metropolitan boroughs, have no real responsibility for the running of the local and personal services. The system proposed by the Commission would place personal, preventive, and environmental health services, welfare and children's services, and housing in the hands of one authority." The Government also proposes to give education as a responsibility to the new boroughs, except for the central area of London, which will have its own education authority. Speaking in Parliament on November 29, Dr. Charles Hill,[3] Minister of Housing and Local Government, said it was the Government's aim to introduce the necessary legislation to put the proposals of the White Paper into effect from April, 1965.

One of the main departures of the White Paper from the report of the Royal Commission is to aim at fewer "Greater London Boroughs" than the 51 suggested by the Commission. The Government thinks that the minimum population of a London borough should be around 200,000, and others could be larger. This would go some way, but nothing like far enough, to meet the proposals[4] of the Council of the B.M.A. The special committee which drew up these proposals on the report of the Royal Commission recommended that there should be five to eight groups of "united boroughs" each with a single medical officer of health under a single health committee, and each of these would administer the entire local authority health services within the boroughs so grouped together. It would follow that there would be one executive council for each united borough. The same committee is meeting again on December 13 to consider the White Paper. To avoid a multiplicity of executive councils the General Medical Services Committee has made the specific recommendation[5] that there should be one for the central area of London and five for the peripheral areas (each with a population of 1¼ to 2 million).

When commenting on the Royal Commission's report we mentioned[6] the unsettling effect on the staff of knowing that their local authority was doomed to disappear or to have its activities curtailed. Admittedly other members of the public health service in the boroughs will find interest and responsibility added to their work, but under the new proposals many medical officers of health and their assistants (not to speak of senior health visitors, district nurses, and midwives) will change their status and their employers, and some may see their offices abolished. This important and so far neglected aspect of the Government's proposals will no doubt receive the close attention of the B.M.A. and the Society of Medical Officers of Health.

[1] *Report of the Royal Commission on Local Government in Greater London, 1957–1960*, H.M.S.O., London, 1960.
[2] *London Government—Government Proposals for Reorganization*, 1961, H.M.S.O., London. Price 1s. net.
[3] *House of Commons Official Report*, November 29, Col. 442.
[4] *Brit. med. J., Suppl.*, 1961, 1, 241.
[5] Ibid, *Suppl.*, 1961, 1, 153.
[6] *Brit. med. J.*, 1960, 2, 1298.

THE BELFAST MEETING

Visitors from Britain to the Annual Meeting of the B.M.A. earlier this year had to travel over continents and oceans to reach New Zealand. Next year they will have only St. George's Channel to cross, but Belfast is not likely to be eclipsed by Auckland in the warmth of its welcome to the B.M.A., strong though the competition may be. The provisional programme of the meeting is printed in the opening pages of the *Supplement* this week. The Annual Representative Meeting will be from Thursday, July 18, to Monday, July 23. Mr. Ian Fraser will give his Presidential Address at the Adjourned Annual General Meeting on July 23, and the Scientific Meeting will occupy the next four days.

There will be a break with tradition next year in that there are to be no meetings of Scientific Sections at Belfast. The Scientific Meeting will consist of symposia, panel discussions, and plenary sessions on subjects which have been carefully chosen to appeal to a wide audience.

Another attraction of the meeting will be the opportunity to see something of the great developments in hospital building in Northern Ireland. A word of warning is necessary to those who intend to come to the meeting. The holiday season will be in full swing, and not only will it be necessary to book accommodation well ahead but those travelling by sea should apply for sailing tickets as soon as possible.

Sir Howard Florey was re-elected President of the Royal Society at the Society's anniversary meeting on November 30.

SUPPLY OF DOCTORS

BY

J. R. SEALE, M.A., M.D., M.R.C.P.

In the early years of the National Health Service the number of fully trained young British doctors exceeded the number of vacancies for permanent positions in the Service. In view of the surplus of doctors which existed at the time, the Willink Committee was set up in 1955 to consider on a long-term basis the number of medical practitioners, and the intake of medical students, which would be required in the future. The Committee[1] concluded that up till 1955 medical schools in Great Britain had not been producing too many doctors, but that after 1961 a reduced output of doctors from the schools would suffice. They therefore recommended in 1957 an immediate reduction in the intake of medical students by 10%.

The Willink Report was widely acclaimed at the time. If there was anyone who dissented he did not publish his views. Indeed, examination of the intake of the medical schools shows that substantial reductions had already been made at many schools before the Report was published.

When the Royal Commission on doctors' pay reported early in 1960[2] the majority of the members accepted the conclusions of the Willink Committee. They stated that, as the supply of doctors in Britain was reasonably close to requirements, there was no need to raise medical incomes in the National Health Service with the purpose either of attracting more young people into medicine or of dissuading doctors from emigrating. Professor Jewkes alone dissented from this view. In his memorandum of dissent he published the number of medical students in training from 1950 to 1958 and showed the steady decline in numbers. By 1958 the number of medical students was almost back to the pre-war level, although university students in all faculties had doubled. He stated that it would be imprudent to be overconfident about the continued supply of doctors.

On September 3, 1960, Professors Lafitte and Squire, in their paper "Second Thoughts on the Willink Report,"[3] concluded that the recommendation of the Willink Committee to reduce the intake of medical students was an error, and they predicted that unless immediate action was taken a crisis in the supply of doctors would emerge around 1965.

Earlier this year I published a graph indicating the output of medical schools of the British Isles each year from 1886 to 1959.[4] After considering the age distribution of doctors in the medical profession I concluded that in the next five years there would be a deficit of doctors—that is, replacements of young British doctors would be inadequate to keep up with losses through death and retirement. In October I suggested that Professors Lafitte and Squire had been too optimistic and that a crisis in the supply of doctors had already arrived in nearly all segments of British medical practice.[5]

In the debate in the House of Lords on November 29, 1961, it became abundantly clear from the evidence which was presented that much of the medical work in National Health Service hospitals is now carried out by doctors born and trained overseas, mostly from the underdeveloped countries. Lord Evans suggested that only half of all emergency surgery in our hospitals is now being undertaken by surgeons trained in Britain.[6] Furthermore, signs of failure in the supply of principals in general practice, and of consultants in anaesthetics, radiology, psychiatry, and E.N.T. surgery, are now apparent.[7] To deal with the situation the Government has announced that it is satisfied that the intake of preclinical students should be raised by 10% above the level recommended by the Willink Committee. The Chief Secretary to the Treasury has asked the University Grants Committee to consider with the universities the implications of the Government's conclusion.[8] These events are reported in *The Times* of November 30 under the headline: "Shortage of Doctors to be Remedied."

I suggest that the action which the Government has taken is, for practical purposes, irrelevant to the situation. Furthermore, I suggest that the number of British doctors in practice in this country has already been falling for several years and will continue to fall for many years. A fall in the number of doctors in practice in Britain has never occurred before in the twentieth century, apart from during the highly abnormal years of the two world wars. The medical profession and the N.H.S. are thus faced with a totally new situation—a situation of a type which nobody in Britain has had any experience in handling. It is unlikely that the conventional ways of thinking about the medical staffing of the N.H.S., which were appropriate to the years of surplus, will have much relevance to the lean years ahead.

As everybody knows, and is frequently told, the number of doctors in the N.H.S. has increased substantially since 1948. However, as the accompanying Charts show, increase has fallen away progressively in recent years. Expansion in the number of doctors in general practice in England and Wales (Fig. 1) has not kept up with expansion of population since 1957, because an increase of over 100 G.P.s is required annually to keep the general practitioner/population ratio constant. The number of principals has increased faster than population, but this has been achieved at the expense of a steadily declining number of assistants.

Expansion in senior specialists (Fig. 2) also has failed to match population expansion since 1957, because an increase of 50 specialists a year is required to keep the

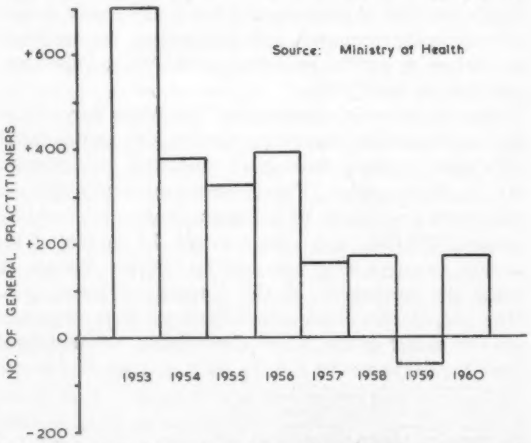

FIG. 1.—Increase in number of general practitioners over preceding year. England and Wales, 1953–60. Note: Includes principals, assistants, and trainee assistants.

specialist/population ratio constant. It is true that the number of consultants has expanded more rapidly than population—but only by decreasing the number of senior hospital medical officers by 264 since 1957. Much of the expansion of consultant staff in recent years has been achieved by changing the status of senior hospital medical officers to that of consultant, not by increasing the total number of senior specialists. As the Royal Commission on doctors' pay pointed out, in the years 1954–7 nearly 300 S.H.M.O.s were appointed consultants—" broadly speaking, one so promoted for every two senior registrars promoted to consultant."[9]

The most substantial increase in the number of doctors in the National Health Service since 1953 has occurred among junior hospital staff, but even there expansion fell practically to zero during 1959–60 (Fig. 3). Between 1957 and 1960 junior hospital doctors increased by 465, but we know from the Platt Report that by mid-1960 there were 3,628 doctors in junior posts who were born overseas.[10] Nobody knows the numbers in earlier years, but there is little doubt that during the three years 1957–60 all the increase in junior doctors resulted from an increase in the number of doctors from overseas staffing the hospitals. I would go further—I would suggest that there has been a falling number of British-trained doctors in junior hospital posts and that all the modest expansion in general practitioners and senior specialists since 1957 has been at the expense of declining numbers in the " pool " of British-trained doctors in junior posts.

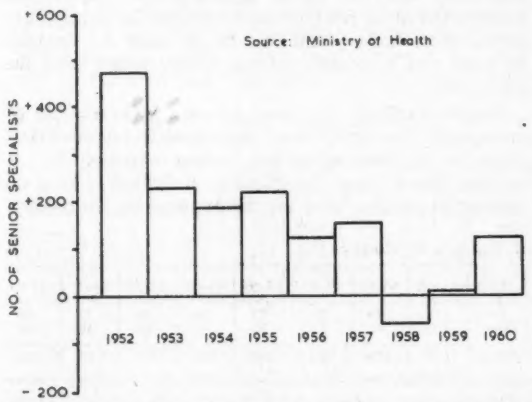

FIG. 2.—Increase in number of senior specialists over preceding year. Great Britain, 1952–60. NOTE: Includes consultants and senior hospital medical officers.

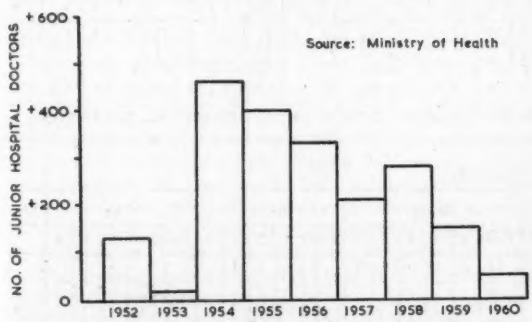

FIG. 3.—Increase in number of junior hospital doctors over preceding year. Great Britain, 1952–60. NOTE: All grades below and including senior registrars.

If there has been no expansion in the number of British-trained doctors in the National Health Service since 1957 where have all our young doctors gone? The output of the medical schools during these years has exceeded the wastage of elderly doctors by 500 or so, yet there has been no expansion. This must be because so many of the men who have qualified since the end of the war have chosen to practise outside their native land, particularly in Canada, the U.S.A., and Australasia. Many of the women cease to practise medicine altogether shortly after leaving medical school. There are no signs that young British doctors are proposing to act differently in the future, even though the rate of retirement of elderly doctors is now rising rapidly.

If the rate of loss of our newly qualified doctors continues at that prevailing in the last decade the National Health Service will have to adjust itself to rapidly falling numbers of British doctors in it. Increasing the intake of medical students is no solution to a problem which flows from the loss of doctors after qualifying, and staffing the N.H.S. with doctors from the underdeveloped countries has its disadvantages.

If the 10% increase in the intake of medical students proposed by the Government takes place, then after 1968 output of doctors will rise by 170 a year. But, since 1955, 220 British doctors have been settling in Canada alone each year. If this loss could be stopped the immediate increase in the supply of British doctors would be greater than the increase resulting from the Government's proposals, which, anyhow, will take seven years to become effective. Young British doctors will remain in the N.H.S. only if conditions of service are reasonably attractive. By their actions, rather than by their words, they have shown that they are unattractive. Up till the present the Government, and many leaders of the medical profession, have failed to see that this is so. But as the failure in the supply of doctors sweeps through the National Health Service and the medical profession like a hurricane, even the sand in which our leaders have buried their heads is being blown away.

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4 Seale, J. R., *Brit. med. J.*, 1961, **1**, 203.
5 Seale, J. R., *Brit. med. J. (Suppl.)*, 1961, **2**, 171.
6 *House of Lords Debates*, vol. 235, No. 15, Col. 1154.
7 Ibid, Col. 1140.
8 Ibid., Col. 1202.
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10 *Medical Staffing Structure in the Hospital Service, 1961*, p. 32.

Individual foil packing is usually regarded as an excellent means of preventing deterioration during normal shelf life, but a sample of aspirin tablets for children packed in this way showed excessive aspirin decomposition, numerous crystals of free salicylic acid being evident on the surface of the tablets beneath the foil pack. The content of free salicylic acid, expressed as a percentage of the total aspirin present, was 3.3%: by comparison the maximum permitted by the *B.P.* for soluble aspirin tablets is 0.16%. Stocks were withdrawn from sale and returned to the makers. Better formulation of the product or an improvement in the foil-sealing process was clearly essential. (*Report of the Second Quarter, 1961*, City of Birmingham Public Analyst.)

HOUSING IN LONDON

AN ANALYSIS OF THE LIVING CONDITIONS OF 503 FAMILIES IN HAMMERSMITH

BY

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About a year ago I was consulted by a patient who suffers from psoriasis. He is employed as a carpenter by a teaching hospital (not in this area of London), and he had been attending the dermatology out-patient department there for some time. At his last attendance he had been given treatment which involved a daily bath—but he had no bath at his home. I was not surprised that this was so, for I knew that bathrooms were a relative luxury in Shepherd's Bush; but when I mentioned this story to a friend at hospital he seemed surprised at the lack of what are regarded as essential amenities. I therefore thought it would be worth while making a more detailed analysis of the living conditions of my patients.

My practice is mainly in Shepherd's Bush, part of the Metropolitan Borough of Hammersmith in the west of London. Local landmarks are the B.B.C. television studios, and, medically, Hammersmith Hospital and Queen Charlotte's Hospital, the latter being at the other end of the road where my surgery is situated. The majority of the houses in the immediate vicinity were built at the turn of the century. Here and there are new blocks of flats, mainly small council developments. Only a small part of the neighbourhood (two small roads) are officially designated slums, and they are at present being cleared preparatory to being redeveloped by the Borough Council. The large estate built by the London County Council at the White City just before and after the last war is about half a mile due north of my surgery, and I have few patients from that estate.

It has not been possible to survey the whole practice—indeed, that would be wellnigh impossible, for it is constantly changing. Approximately one-third of my patients have been registered with me less than a year. In the last twelve months about 1,100 new patients signed on my list, while in the same period about 500 left. For the same reason an age–sex index is accurate only for the day it is completed, and as yet I do not know if the age distribution of the new patients is the same as that of those who have gone elsewhere. Table I shows clearly how the practice is dominated by young children and their parents. How these young mothers cope in the face of difficulty is a great tribute to them and a rebuke to us as a community.

Material Investigated

I decided to collect information from about 500 families. I asked questions of every patient I saw until I had the requisite total. I excluded the 12 young men who said they were living in "digs" (that is, they lived in the home of a "landlady" who prepared whatever meals they ate at home), but I included the 88 patients who said they lived alone but did their own housekeeping. I defined a family as any group sharing the same cooking facilities and food, and who regarded themselves as a family; under this definition lodgers were excluded from the total of members of the family (when the lodger himself presented as the patient he was not included in the survey and he was not asked for any further details). A "family" usually consisted of a husband and wife (including those not actually legally married), together with their children and frequently one or more grandparents. Sometimes cousins and other relatives were counted in, particularly in the West Indian families. In all cases the decision on who was a member of the family rested with the informant.

Shepherd's Bush is an area where a large number of immigrants live, and I have attempted to record differences in the housing of the various nationalities. I realized that a racial classification is difficult, but in no case did the patient have any doubt about his nationality.

TABLE I.—*Age and Sex of Patients in Practice*

	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	75+
Male	284	88	93	92	197	271	191	130	114	89	77	73	50	29	17	29
Female	245	98	86	110	246	210	138	102	103	91	83	70	60	68	46	81
Total ..	529	176	179	200	443	481	329	232	217	180	160	143	110	97	63	110

TABLE II

No. in Family:	One						Two						Three									Four							
No. of Rooms:	Ttl.	1	2	3	4	5	Total	1	2	3	4	5	Total	1	2	3	4	5	6	7	8	9	Ttl.	1	2	3	4	5	6	7	8
English ..	45	28	12	3	1	1	72	12	43	9	3	5	65	7	30	17	4	3	1	1	1	1	51	6	9	13	12	6	1	3	1
Irish	12	12					20	16	2	2			20	12	4	3	1						10	2	6	1		1			
W. Indian ..	18	17	1				40	31	8	1			12	6	6								16	6	9	1					
W. African ..	10	10					4	3	1				2	1			1						0								
Miscellaneous	3	2	1				4	3	1				17	7	6	2		1	1				5	1	2	1		1			
Total ..	88	69	14	3	1	1	140	65	55	12	3	5	116	33	46	22	6	4	2	1	1	1	82	15	26	16	12	8	1	3	1

TABLE II (*Continued*)

No. in Family:	Five							Six							Seven						Eight					Nine					Ten
No. of Rooms:	Total	1	2	3	4	5	7	Total	1	2	3	4	5	7	Total	2	3	4	5	6	Total	4	5	6	9	Total	3	6	8	9	2
English ..	29	1	8	5	9	5	1	6			2	2	1	1	11	2	1	3	4	1	3	1	1	1		1		1			
Irish	4	1	3					4		2	2				0						1				1	3	1		1	1	
W. Indian ..	6		3	2	1			2		1	1				0						0					0					1
W. African ..	0							0							0						0					0					0
Miscellaneous	3		1	1		1		3	1	2					0						0					0					
Total ..	42	2	15	8	10	6	1	15	1	5	5	2	1	1	11	2	1	3	4	1	4	1	1	1	1	4	1	1	1	1	1

The four major groups living in this area are the English, the Irish, the West Indian, and the West African. There are not many Scots, Welsh, or Northern Irish families on my list, and the term "British" is hard to define. I finally decided to include in the "English" group only families where both parents had been born in England. The "Irish" group refers to families from Eire and not from Northern Ireland. In the "West Indies" group I did include a few families from British Guiana. The "Miscellaneous" group includes the Scots, the Welsh, the Northern Irish, and families from other parts of the Commonwealth or the rest of the world. There were also a few families where intermarriage made my classification impossible; I put them with the miscellaneous.

Only just over half the families (56%) were English. Seventy-four families (one in seven of the total) were Irish. Ninety-five (nearly one in five) were from the West Indies. Sixteen (3%) came from West Africa. There were 35 families in the miscellaneous group. Table II shows the sizes of the families in each national group. From it can be calculated that 1,499 people came into this survey. They cannot all be called patients, because for ethical reasons I did not ask the informants who of their family was or was not registered with me. However, in Shepherd's Bush, unlike other districts, most people seem to choose the same doctor for all members of the family.

Nationality of Patients Surveyed

Of the 503 families who finally came into the survey, 78 (15.5%) occupied a house (either owned or rented). Of the English families, 18% had a house, but only 12% of the Irish and West Indians (Table III). None of the West African families had a house, but few of them propose to stay in England permanently, even though many have been here several years already. Quite a number of English families had Council houses, but none of the other national groups had. All the Irish families who had a house took in lodgers, usually young Irish labourers whose rent helped to pay the mortgage. All the West Indian families with a house sublet rooms or shared their property with one or more other West Indian families (mostly cousins).

TABLE III.—*Housing Accommodation*

	Unfurnished		Furnished		House		Total	
	No.	%	No.	%	No.	%	No.	%
English	192	67·8	39	13·8	52	18·4	283	56·3
Irish	13	17·6	52	70·3	9	12·1	74	14·7
W. Indian ..	3	3·2	80	84·2	12	12·6	95	18·9
W. African ..	1	6·2	15	93·8	—	—	16	3·2
Miscellaneous ..	10	28·6	20	57·1	5	14·3	35	6·9
Total ..	219	43·5	206	41	78	15·5	503	100

The other 425 families were almost evenly divided between those who had a furnished "flat"* and those who rented one unfurnished. This difference will mean most to those who are aware of the intricacies of the Rent Acts; for example, security of tenure is assured only to those who have an unfurnished flat whose rateable value is less than £40 and who have lived in it continuously since 1957. Of the English families in flats 85% managed to find one unfurnished, but 70% of the Irish, 84% of the West Indian, and 94% of the West African families were in furnished apartments. Here the tenant can appeal against his rent to a tribunal, in which case he is given only three months' security of tenure.

*The term "flat" is used here to include all accommodation that is not a complete house. Rarely does it imply, as will be shown, a self-contained apartment in either a block or a proper conversion of a house.

Deficiency of Accommodation

The Englishman's home is his castle, but to be a castle it ought to be possible to shut a door and know that only your own family is behind it. Of the 503 families I asked, over two-thirds (68%) did not have self-contained accommodation. They had no front door of their own. Even among the English less than half (44%) lived in a self-contained flat or house. Among the 185 immigrant families only six had complete privacy when they wanted it.

In what other ways was the accommodation deficient? How many families, for instance, had a bathroom? Tables IV and IVa give this information for the various groups. Altogether 44% of my families had no access to a bathroom in the house they lived in; most of the other 56% had to share their asset with another family (except those few families in self-contained accommodation, which also possessed a bath). Forty-eight per cent. of the English families had no bathroom, and 57% of the Irish were in the same position. But only 31% of the West Indian families and a similar proportion of the West Africans were without a bathroom. Oddly enough, more families in furnished accommodation (65%) than those (42%) whose flat had been rented unfurnished had access to a bathroom. As expected, the highest percentage of bathrooms was found among the families having their own house, though even 27% of these were still without one.

No family admitted to being without access to a lavatory (W.C.), though often it was outside, which cannot be very comfortable in winter. Less than half (47%) of the families had their own lavatory (Tables IV and IVa); the rest had to share with another family. Almost all the West African families (94%) had their own W.C., and 59% of the English similarly did not have to share. Only 42% of the Irish had this degree of privacy, and as few as 10% of the West Indian families.

In the Table several families who have a house are shown as sharing a lavatory. This always implies that there is another family unit in the house with them: as explained above, many families join together to buy a house.

The kitchen is where two families sharing any part of the accommodation are most likely to find friction, and over 80% of my families had managed to get a kitchen of some sort of their own (Tables IV and IVa), even though it was only (as is so often the case) a gas-stove on the landing (see Fig.). Almost all the English families (96%) were in this position; and even the Irish (who

TABLE IV

	Total	W.C.				Kitchen				Bathroom			
		Own		Shared		Own		Shared		Available		Not Available	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
English	283	167	59	116	41	271	96	12	4	147	52	136	48
Irish ..	74	31	42	43	58	57	77	17	23	32	43	42	57
W. Indian	95	9	9	86	91	48	51	47	49	66	69	29	31
W. African	16	15	94	1	6	9	56	7	44	12	75	4	25
Misc. .	35	16	46	19	54	26	74	9	26	25	71	10	29
Total	503	238	47	265	53	411	82	92	18	282	56	221	44

TABLE IVA

	Unfurnished								House							
	W.C.				Kitchen				Toilet				Kitchen			
	Own		Shared		Own		Shared		Own		Shared		Own		Shared	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
English	114	59	78	41	190	99	2	1	48	92	4	8	51	98	1	2
Irish	11	85	2	15	13	100			9	100			9	100		
W. Indian	2	67	1	33	2	67	1	33	2	17	10	83	7	58	5	42
W. African ..	1	100			1	100										
Miscellaneous ..	6	60	4	40	10	100			4	80	1	20	5	100		

are not so lucky with their bathroom or lavatory facilities) did not often have to share a kitchen: 77% had their own. On the other hand, nearly half the West Indian (49%) and West African (44%) families have to share cooking facilities. Where two races share a "kitchen" (often just a stove on the landing) their different foods and spices often spark the quarrel which might not otherwise have been ignited.

What about the actual living accommodation itself? From personal observations when I visited them I already knew that many families have to sleep in the room they have been sitting and eating in—and in some cases they also have to wash themselves and cook in the same room. What I did not know was just how common an occurrence this was. Table II gives the details of how cramped families of different sizes are. Not unexpectedly, more than three-quarters of those who lived alone were found to have only one living-room. But even among the couples who lived together (usually husband and wife, but sometimes two girls or two men sharing a flat) nearly half also had only one room (65 of the 140 couples—46%). This is reasonable; but not so happy was my finding that one in five of the families with three, four, or five members were just as limited in living-space and could get only one room for the whole family to live in. The English have not fared too badly: only 10% of the 137 families with three to five members were so cramped, but 40% of the 69 Irish and West Indian families of this size had to live in one room. Table V emphasizes this racial difference by showing the mean number of living-rooms available to families of different sizes within each national group.

A "kitchen" on the landing.

TABLE V.—*Mean Number of Living Rooms in Families of Different Sizes and Different Nationalities*

	Size of Family							
	1	2	3	4	5	6	7	8
English	1	2	2	3	4	4	4	5
Irish	1	1	1	2	2	2–3		
W. Indian ..	1	1	1–2	2	2	2–3		
W. African ..	1	1	1					
Miscellaneous ..	1	1	2	2	3	3		

Rents

Finally, I looked at the rent my patients had to pay for their home. Some owned their home; others by virtue of their employment (for example, school caretakers) had free accommodation. Rents will naturally be greater for furnished than for unfurnished flats, and the Rent Acts emphasize this difference (only unfurnished flats have their rents controlled). The majority of immigrants live in flats, and so I propose to compare only these rents. The mean rent paid by an English family for a flat is between 30 and 40 shillings a week, but the immigrants have to pay between 60 and 70 shillings. However, the great majority of the immigrants are in furnished flats, and for such accommodation the English also pay a mean rent of 60 to 70 shillings a week. So few immigrant families (only 17) live in unfurnished flats that it is not reasonable to draw definite conclusions, but their mean rent is 50 to 60 shillings a week as compared with 30 to 40 shillings paid by the English in this position. This low rent paid by the English for unfurnished flats reflects their ability to get either a council flat or a rent-restricted flat in a house which, incidentally, their family have often occupied for many years.

The difference can best be brought out by considering the extremes of rents paid in this district. Forty-seven per cent. of the 231 English families living in flats pay less than 30s. a week in rent, and only 5% pay more than £5 a week. But among the 154 immigrant families in flats only 3% pay under 30s. a week, while 13% pay over £5. Only one English family in the higher-rent group had unsatisfactory accommodation. This is a family of five who had one living-room, a gas stove on the landing, and shared the lavatory with the other three families in the house. There was a bathroom, but it was unusable. It is perhaps not irrelevant to add that this family had been evicted from a council flat for some reason or another (their excuse and the council's explanation did not tally). Only one immigrant family paying more than £5 a week had

a self-contained flat. All the four Irish families in this group had three living-rooms and a bathroom as well as their own kitchen, indicating that they got some value for their money. But only three of the eighty-three families from the West Indies paying a high rent aspired to such luxury, and they had to pay, respectively, £6 6s., £6 10s., and £7 7s. a week. Incidentally none of these three families had their own bathroom or W.C., but they did get their own kitchen.

Comment

I have already mentioned that this area is not officially designated a slum. How much overcrowding there exists will depend on what definition of "overcrowding" is used. The official standards permit up to two people in one room, three people in two rooms, five in three rooms, and so on. Only living-rooms are calculated, and children between the ages of 1 and 10 years count as half a person; babies under the age of a year do not count. When I asked my patients for information for this survey I deliberately avoided the official approach, and I did not attempt to assess the legal overcrowding which I know, from what they tell me, is often hidden from officials.

It is of course right to point out, as can be seen from the practice age–sex register (Table I) that young families form a large proportion of my practice. Perhaps as the children grow up the family is able, either through the local authority or by its own efforts, to get a flat or house more adequate for its needs; I hope this is so, though I do not know whether it is or not.

What does the classification by nationality bring out? In essence it is as follows, and my findings in the survey are confirmed by my own experiences of cleanliness and so on when I visit their homes. The English consider a separate kitchen to be top priority; the West Indians try to find a flat in a house with a bath; while the Irish seem to get the worst of practically everything.

As a general practitioner I am in a way an agent of the Welfare State. Through me my patients are able to obtain any drug, however expensive. I can arrange their admission to hospital or get them a convalescent holiday if they need it. I can introduce them to the National Assistance Board when they are short of money. But, however inadequate their housing, there is nothing I can do about it. I have long realized the futility of medical recommendations to the local authority; I know they have no accommodation to spare, however desperate the need. What worries me is the apparent perpetuation of the problem. About seven years ago, when I was new to general practice, I came across a family of seven living in one room. I was so horrified that I wrote a very stiff letter to the L.C.C. They acted swiftly, and the family were given a house on a new estate. One Friday evening the mother came to see me to say good-bye and to thank me for my efforts. The next morning a new patient came to see me, bringing with her several medical cards—for herself, her husband, and her five children. She said they had moved into the room vacated by Mrs. X, and would I give her a letter to the Council like I had given the other lady.

The publication of the *Annual Report of the Victorian Bush Nursing Association 1960–1961* celebrates half a century of service in the Australian bush. The first centre was established at Beech Forest in February, 1911.

DISEASES OF GENETIC AETIOLOGY

CONFERENCE AT GLASGOW

[FROM A SPECIAL CORRESPONDENT]

A conference on diseases of genetic aetiology was held in the Faculty of Physicians and Surgeons, Glasgow, from November 15 to 17 under the auspices of the Glasgow Postgraduate Medical Board.

Neoplasia and Hyperplasia

After an introduction by Professor L. S. PENROSE, F.R.S., under the chairmanship of Dr. J. H. WRIGHT, Dr. W. M. COURT BROWN opened the first session with a paper on the role of genetic change in neoplasia. He discussed the possible role of such change both in the initiation of the neoplastic process and also in its evolution from the early initial changes in a cell, or group of cells, right through to the stage of clinical cancer. This discussion included a general survey of cancer susceptibility and the problem of ageing and carcinogenesis.

Dr. C. A. CLARKE described two families in which an extremely high incidence of oesophageal cancer occurred associated with tylosis. He postulated that the striking association of these two conditions might well be due to a single gene mutation. The present position of chromosome aberrations in myeloid leukaemia both in the chronic state and during its acute transformation was dealt with by Dr. A. G. BAIKIE. He also discussed the possibility that certain drugs might selectively act on certain cell lines which could be distinguished on a chromosome basis.

Biochemical Lesions

In the afternoon session, under the chairmanship of Professor T. SYMINGTON, some biochemical lesions of genetic aetiology were discussed. Professor G. PONTECORVO, F.R.S., reviewed the history of studies relating genes to the synthesis of enzymes in particular and proteins in general. He referred to the classical studies of Garrod on inborn errors of metabolism, which, he felt, had been published at a time when neither medicine nor genetics was ready to appreciate them fully. Garrod's concept on one-gene-one-enzyme was an oversimplification, and we now had evidence of the activity of regulator genes which influenced other genes without the mediation of a protein synthesized for the purpose. Other recent advances had come from the analysis of the genetic material itself with a reawakening of interest in D.N.A. and appreciation of its heterogeneity. Many of Professor Pontecorvo's points were illustrated by subsequent papers by Dr. H. LEHMANN on the haemoglobinopathies; by Dr. A. S. DOUGLAS on haemophilia and related coagulation defects; and by Dr. A. GOLDBERG on the porphyrias.

Amino-acid Metabolism

Under the chairmanship of Professor PONTECORVO, the session on genetically determined biochemical lesions was opened by Dr. J. P. JEPSON, who gave a comprehensive general account of the amino-acidurias much appreciated by those who had no specialized knowledge of this field. He followed this by a discussion of Hartnup disease, a rare condition the occurrence of which was consistent with its being determined by an autosomal recessive gene. The only constant physical finding was a photosensitive rash identical with that found in pellagra. However, paper chromatographic study of the urine of individuals with Hartnup disease showed that they were excreting large amounts of a wide but characteristic range of amino-acids. This was thought to be due to a disorder of amino-acid transport into all cells of the body, particularly those of the renal tubules and the jejunum. Dr. Jepson stressed the need to carry out chromatographic analysis of the urine of all patients presenting with symptoms of pellagra, as this was the only way a differential diagnosis between pellagra and Hartnup disease could be made.

Dr. L. I. WOOLF described maple syrup urine disease, another rare enzyme defect whose mode of inheritance is consistent with its being determined by an autosomal recessive gene. Within a few days of birth children suffering from this disease failed to suck and then rapidly deteriorated and died. On necropsy the only significant finding was that the white matter of the brain was deficient in myelin. The urine of these children had a characteristic "maple syrup" smell and it was found that they excreted excessive leucine, isoleucine, and valine and their keto acids. Dr. Woolf suggested that if the diagnosis was established early enough it might be possible to prevent the onset of the symptoms of maple syrup urine disease by feeding the patient a diet low in the three relevant amino-acids.

Malformations Due to Chromosomal Aberrations

Under the chairmanship of Professor D. F. CAPPELL, Professor PENROSE opened the session on chromosome aberrations with a general paper on the mechanisms involved in their production, setting the stage for the more detailed papers which followed. Dr. M. FERGUSON-SMITH dealt with abnormalities of the sex chromosomes, while Dr. J. L. HAMERTON dealt exclusively with chromosome 21 and its inheritance both in cases of "classical mongolism" and in cases of "translocation mongolism." It was left to Dr. J. H. EDWARDS to deal with the aberrations of the remaining chromosomes. He began by defining the very large areas of ignorance in this subject, many of which, he pointed out, were caused by the fact that the size and morphology of the human chromosomes were such as to give rise to the maximum possible amount of confusion. Dr. Edwards then proceeded to what one knew, and discussed the two trisomic conditions of the autosomes (excluding mongolism) which have so far been found to be associated with clinical syndromes—namely, trisomy 17-18 and trisomy 13-15. He concluded his paper with a brief discussion of translocations and deletions and a plea that detailed blood-grouping studies should be carried out on all individuals found to have an autosomal aberration.

Dr. B. LENNOX concluded this session with a brief summary of present knowledge and future prospects in the field of human cytology and looked forward to the day when he could map genes on human chromosomes with the certainty with which this can now be done in *Drosophila*.

Malformations Due to Single Genes

The last session, under the chairmanship of Professor T. F. RODGER, was devoted to discussion of congenital malformations due to single genes. Dr. J. H. RENWICK discussed the multiple effects of single genes with reference to some of the conditions described in the papers which followed. He justified the study of such rare abnormalities by explaining how rarity was commonly associated with genetic simplicity. In any case, some 10% of congenital abnormalities in man were due to the action of single genes. Dr. Renwick pointed out how evolutionary, environmental, and genetic factors might modify and even obscure the primary action of a gene.

Dr. L. FISCH discussed the white forelock syndrome. The features of this syndrome were deformity of the eyelids, deafness which was often unilateral, failure to develop pigment in all or part of the iris, a rather massive lower jaw which was only manifest in cases showing the eyelid deformity, and a white forelock. He stressed that while this latter feature was the most striking it was also the rarest. The syndrome was common and was thought to be determined by an autosomal dominant gene which in some way affected the development of tissues derived from the neural crest. The white forelock syndrome had been estimated to be the cause of as much as 3% of all cases of hereditary deafness, and as this estimate was based only on cases of severe bilateral deafness it was obviously a considerable underestimate.

DOCTORS' HOBBIES EXHIBITION

The fifth Doctors' Hobbies Exhibition, organized by Benger Laboratories Limited, was held in the Great Hall of B.M.A. House from December 4 to 8. Over 400 doctors exhibited, more than 200 for the first time.

The three most outstanding exhibits were chosen from the first-prize winners in each class. The first prize (£75) went to Mr. F. R. Neubert (Guernsey) for two portraits in the photographic section. Dr. F. P. T. Drake (Chertsey)

[*Barratts Photo Press, Ltd.*

"Institutional Neurosis," by Dr. R. Barton.

won second prize (£50) for his model of H.M.S. *Wolvertown*. The third prize (£25) went to Dr. D. Latto (London) for his entry on the 2s. British postage stamp in the philately class.

The first-prize winners in the various classes were: *painting, oils:* Dr. R. Barton (Colchester); *watercolours:* Dr. J. P. Raw (Cheam), who also won first prize in the *home handyman* class; *sculpture and wood carving:* Dr. A. W. Strek (Bradford); *woodwork:* Dr. Marie R. Campkin

[*Barratts Photo Press, Ltd.*

General view of the Doctors' Hobbies Exhibition from the Gallery of the Great Hall.

(Hatfield); *metalwork and engineering:* Dr. J. M. Benjamin (Waltham Cross); *ceramics:* Dr. B. J. Sherry (Oxford); *electrical:* Dr. N. H. Barley (London); *inventions:* Dr. W. R. Wilson (Doncaster); *photographic transparencies:* Dr. E. H. Franks (Dundee); *general photography:* Dr. E. C. Dayus (Buckhurst Hill); *collections:* Mr. R. C. Bell (Gosforth); *antiques:* Dr. C. E. D. H. Goodhart (Surrey); *natural history:* Dr. J. T. H. Knight (Horsham); *authorship:* Dr. G. Ward (Sevenoaks); *musical composition and performance:* Dr. G. H. Pagdin (Sheffield); *embroidery and crochet:* Dr. Betty R. Warltier (Stanmore); *knitting and sewing:* Dr. R. MacDonald Rowland (South Ockendon); *gardening:* Dr. A. E. S. Wood (New Barnet); *miscellaneous:* Dr. B. F. Martin (Sheffield).

SKIN DISEASES AND MALABSORPTION

R.C.P. CONFERENCE

Under the chairmanship of Sir ROBERT PLATT, P.R.C.P., the first Parkes Weber Lecture was given at the Royal College of Physicians on November 17. The chairman opened the proceedings by explaining that in 1959 the College received a gift from Dr. F. Parkes Weber. It was for the purpose of arranging a lecture, or to be used as a prize for a lecture or essay, the exact use being left to the discretion of the College.

The conference began with the Parkes Weber Lecture by Dr. G. C. WELLS (London) on skin disorders in relation to malabsorption and malnutrition. Dr. Wells observed that though the skin remains intact in extreme starvation and malnutrition marked changes occur in these states. Skeletal deformities and tetany were observed in coeliac disease. The features of hairlessness of face and scalp together with a diffuse pigmentation sometimes affecting the buccal mucous membranes were described in cases of steatorrhoea. One worker had recorded seborrhoeic dermatitis or psoriasis-like changes in 20% of steatorrhoea patients. Some of Dr. Wells's cases showed non-specific widespread eruptions of eczematous type preceding clinical steatorrhoea by two or three years. These cases responded to replacement therapy with vitamin supplements, gluten-free diet, iron preparations, and proteins, and with the general improvement in health the rash disappeared.

The President of the College then presented the Parkes Weber medal to Dr. Wells.

Stress and Cell Replacement

Professor W. S. BULLOUGH (London) said that when adequately fed mice were subjected to stress their epidermal cells showed reduced mitotic activity. This was due to the inhibition of the first stage of cell division, though the cells had been able to build up adequate stores of energy. As soon as the effects of stress were removed, large numbers of cells underwent mitotic division. This was due to adrenaline. And adrenaline itself could produce the same depression of mitotic activity as was seen on exposure to stress. Long-term stress could completely inhibit cell replacement. In daily life stress was continually present, but at night during sleep the inhibition of mitotic activity was removed and cell replacement proceeded fast. Mitotic figures in human epidermis could be seen in specimens taken from a "stress-free" sleeping subject.

Changes in Mucous Membranes

Dr. J. BADENOCH (Oxford) discussed the glossitis which is seen in patients with vitamin-deficiency states and with steatorrhoea. In the latter the cause was completely unknown and the soreness of the tongue might persist despite all treatment. In anaemias the glossitis might remit after treatment when all other features of the malady had cleared. The histological changes in the mouth of such patients were not constant, and the pain seemed to have no constant relationship to them. One of the most constant findings was loss of melanin. There might be dysphagia in patients with normal mucous membrane in the oesophagus. Iron deficiency might be responsible for some of these changes, for actively growing tissues needed traces of iron. A hypoplastic marrow might take up iron at the expense of the buccal mucous membrane.

Skin Changes in Hypocalcaemia

Dr. M. GARRETTS (Manchester) described four cases of hypocalcaemia associated with skin changes (published by Professor C. E. Dent and himself last year). These were of different aetiology: one patient had permanent hypoparathyroidism after the removal of a non-toxic thyroid adenoma; one had a severe but temporary hypoparathyroidism after the removal of a large tumour of a parathyroid gland: and two had steatorrhoea—idiopathic in one and probably coeliac disease in the other. These patients had a dermatosis which could be related in onset and severity to the level of the calcium in plasma (or serum). Seven further hypocalcaemic cases had also been studied in which a rash was related to the serum calcium level.

It seemed immaterial by what means the level of the serum calcium was restored to normal—whether by the return of the patient's own parathyroid function or injections of calcium gluconate, parathormone, or derivatives of vitamin D. The rash responded equally well to all.

CONFERENCE ON ARTERIAL DISEASES

NUFFIELD INSTITUTE OF COMPARATIVE MEDICINE

[FROM A SPECIAL CORRESPONDENT]

A conference on arterial diseases convened by the Nuffield Institute of Comparative Medicine was held at the Zoological Gardens on November 22, under the chairmanship of Sir ROY CAMERON, F.R.S., and attended by invited speakers and guests.

The members of the conference were welcomed by the Secretary of the Zoological Society, Sir SOLLY ZUCKERMAN, F.R.S., who pointed out that for the last 100 years the Society had pursued its own studies in veterinary pathology and had a vast collection of documented necropsy records on an enormous variety of animals. He explained that the Nuffield Foundation was setting up this Institute (see *B.M.J.*, December 2, p. 1508) in the grounds of the Zoological Society for the study of comparative pathology and medicine. One of the main objects of study was the comparative pathology of arterial disease and perhaps also of tumours. The Wellcome Foundation was generously contributing to the Institute.

Natural Disease in Animals

Dr. MARTIN M. KAPLAN (Head of the Veterinary Public Health Section, W.H.O.) suggested that some of the keys to degenerative arterial diseases in man might be found in the comparison of human and animal lesions and that it was important to discover what arterial diseases affected animals in their normal state—the natural diseases as opposed to those induced by experimental methods. He drew attention to some of the possible lines of study; in particular, arterial disease in aged swine, arterial disease in aged birds, and cardiovascular disease in dogs kept under study in colonies till old age. He hoped that perhaps some analogy might be found in the animal kingdom for that peculiar disease of humans, endomyocardial fibrosis. Sir HAROLD HIMSWORTH,

F.R.S., agreed with the importance of studying natural disease in animals after all the work that had been done on experimental disease in animals.

Dr. D. K. DETWEILER (director of Comparative Cardiovascular Studies Unit, Philadelphia) gave an outline of the work in this field going on at present in the U.S.A. Studies were being carried out on lipid metabolism, including the influence of diet and exercise, on thrombotic mechanisms, on experimental arterial disease, and on natural arterial disease in colonies of animals. He mentioned the increasing use of primates, swine, and pigeons as opposed to small rodents. There were at present three large colonies of primates under long-term observation. He postulated three questions that urgently require answers: Are the arterial lesions observed in different animal species really alike in nature? Are aetiological factors common to different animals? Are the natural arterial diseases of animals really equivalent to those of man? He pointed out, furthermore, that we still needed to know the real prevalence of arterial disease in different animal species. There were a number of interesting questions and comments on these topics.

Emphasis Changing to Thrombosis

Professor T. CRAWFORD (St. George's Hospital) outlined briefly the different lesions that occur in human arteries leading up to atherosclerotic occlusion and thrombosis. He discussed the different hypotheses regarding the development of human occlusive lesions and pointed out the recent change of emphasis from age changes and fatty deposition towards thrombosis as the important and crippling factor: a change of attitude that had followed Professor J. N. Morris's studies.

Dr. J. E. FRENCH (Oxford University) described the studies of Sir Howard Florey's group on the arterial lesions of aged swine. Unfortunately, the longevity of swine was dependent on market economics and almost the only creatures available were elderly breeding sows, whose age was in fact probably not really comparable with that of elderly humans. The lesions he demonstrated had an interestingly constant distribution, in many ways similar to those of human atherosclerosis. It was interesting to note the particular severity of atheroma in the arteries supplying the uterus and breasts of breeding sows. The actual lesions seen in swine, though like the human disease in many ways, never reached the degree of severity that in man caused occlusive changes. Pigs might develop atheroma in their coronaries, but they did not thrombose. The pig, however, enjoyed a naturally low blood cholesterol (about 88 mg./100 ml.).

Dog and Man

Professor W. I. B. BEVERIDGE (Cambridge University) gave an outline of the researches now being carried out on atherosclerosis in domestic animals. He then invited the individual workers to present some of their findings. Among those who spoke, Dr. JOHN C. WHITNEY (Edinburgh University) pointed out the remarkable difference between disease of the coronary circulation in man and dogs. Whereas in man the disease was atherosclerosis and affected the proximal parts of the main coronary arteries, in dogs the natural disease affected the smaller arteries running amongst the cardiac muscle. Here there occurred a muscular thickening of the arterial wall with hyaline change, and although thrombosis did not occur the vascular narrowing was severe enough to cause ischaemic fibrosis of the papillary muscles though macroscopic infarcts were not seen. Curiously, this lesion mainly affected the branches of the left circumflex coronary. The lesions described were much more like those seen in the small arteries of human arteriosclerotic kidneys than anything seen in human hearts. In the dog's aorta, which was structurally like the pig's, the normal sclerotic lesion was a purely fibrous one devoid of lipid.

Dr. R. FINLAYSON (St. Bartholomew's Hospital) and Dr. C. SYMONS (Royal Free Hospital) described the results of their studies at the London Zoo in collaboration with Mr. R. N. FIENNES, the pathologist to the Zoological Society. Dr. FINLAYSON showed numerous beautiful illustrations of arterial disease in birds, mammals, and reptiles. Macroscopically the lesions resembled the fatty streaking of the human aorta in young subjects though microscopically the lipid infiltrations were often associated with appreciable fibrous thickening. In all these creatures, however, the coronary arteries were amongst the least affected, and, again, thrombosis was conspicuously absent. Man, however, was at least spared parasitic infestation of his aortic wall with fatal rupture.

Dr. SYMONS found fatty streaking in about 25% of necropsies on mammals and birds, but only rarely in reptiles. It was interesting to note that, in spite of the lipaemia that accompanied egg-laying, hens were no more liable to atheroma than cocks; one was left wondering whether here, too, oestrogens played a protective role. In spite of the restriction of activity imposed by life in a zoo, thrombosis was not seen and there was no apparent difference in the incidence of arterial disease between wild and caged beasts. One wondered whether there was a significance in the relatively frequent atheroma of meat-eating vultures and eagles as compared with its rarity in fish-eating penguins. A final interesting point was that the order of frequency of natural arterial disease in birds, mammals, and reptiles corresponded with the height of their normal blood cholesterol.

Few Answers But Many Questions

The day's papers were briefly summarized by Sir ROY CAMERON and the discussion was opened in a deliberately provocative vein by Sir HOWARD FLOREY, P.R.S. Amongst a number of pertinent questions, he wondered how some fish with a normal blood cholesterol of 1,000 mg./100 ml. managed to escape atheroma. Dr. Z. FEJFAR (head of Cardiovascular Studies Unit, W.H.O.) then outlined the programme of studies and some of the results achieved by the World Health Organization in the international field. The rest of the afternoon session was devoted to general discussion. If we did not find many answers, we at least heard a number of highly pertinent and thought-provoking questions. Finally, Mr. L. FARRER BROWN, director of the Nuffield Foundation, proposed a vote of thanks to the speakers and received from the chairman the warm thanks of all those present for a stimulating day's discussion and their good wishes to Lord Nuffield.

RADIOBIOLOGICAL RESEARCH

Nuclear explosions in the last few months have triggered off a fresh wave of public anxiety about fall-out. It was a good move therefore on the part of the Medical Research Council to invite medical and scientific press correspondents to an "open day" on November 28 at the Council's Radiobiological Research Unit at Harwell. Some 40 correspondents came. The Unit, which is directed by Dr. J. F. LOUTIT, with Dr. R. H. MOLE as deputy director, lies outside the security fence of the Atomic Energy Research Establishment, and, as Dr. Loutit was at some pains to explain, is not concerned with supervising the health of workers at the A.E.R.E. or monitoring local radiation levels. The Unit's job, in the official phraseology, is "to investigate the fundamental action of ionizing radiation on living systems." Nowadays great interest centres, of course, on the delayed effects of radiation and on the long-term effects of quite small doses, so it was hardly surprising to find that some of the experiments are themselves long-term and unlikely to yield quick answers. But the general impression was that highly practical problems are being tackled, some of which are immediately relevant to

clinical medicine. A representative series of nine demonstrations was mounted for the press.

The Unit was established in 1947, at that time within the security fence, but in 1953 it was moved to its present position outside. This has allowed room for expansion. The present staff totals 172, of whom 35 are medically or scientifically qualified. There are sections of physiology, experimental pathology, genetics and cytogenetics, biophysics, radiochemistry and chemistry, and a "director's section."

Effects of Fall-out

Expectedly there were studies in animals of the metabolism of the fission products from nuclear bombs. Rabbits were being fed with short-lived isotopes, such as radioiodine, collected from the air. And in man there were studies of the excretion of strontium-90 and the retention of caesium-137. Less expected was the news that Dr. LOUTIT and two of his colleagues (Dr. G. E. HARRISON and Mr. T. E. F. CARR) have been acting as their own experimental animals and eating a diet deliberately contaminated with radiostrontium. The strontium was given in both bread and milk to see if the vehicle affected the result.

What happens to populations when some of its members are damaged by radiations? This is being tested by Dr. J. GODFREY in a standard population of mice The males of one strain of mice, identifiable by coat-colouring, have their testicles irradiated at varying stages of spermatogenesis, and they are then released among control mice of a different colour in a cage ingeniously designed to permit free breeding. Results are assessed by survival rates and reproductive capacity. Irradiation at a late stage reduces the rate of reproduction, whereas irradiation at an earlier stage has much less effect. Another experiment by Dr. A. G. SEARLE is a study of the effects on genes affecting "overall fitness." For this, the cumulative effect of irradiating successive generations of mice is being investigated by enumerating skeletal abnormalities as compared with those in unirradiated controls. Surprisingly, there were more abnormalities in the unirradiated controls than in the irradiated generations. What the precise meaning of this finding may be is uncertain.

Chromosome Studies

Chromosome studies form a prominent part of the research at the Radiobiological Research Unit. Dr. C. E. FORD and Dr. CONSTANCE CLARKE demonstrated some of their work on human chromosomes, particularly from cases of leukaemia. In Dr. Ford's view up to a half of cases of acute leukaemia may well be found to have abnormal chromosomes. Dr. CLARKE was analysing the chromosomes from two cases of leukaemia, in one of which there was a single abnormality derived presumably from a single aberrant cell and in the other multiple abnormalities. Studies of the effects of simple physical factors, such as type and dose-rate of radiation, temperature, and oxygen concentration, in modifying cellular response to radiation, are being made by another section in the more easily observed chromosomes of the root-tip of the bean.

Background to Radiotherapy

Another group of experiments is concerned with the reactions of organ cultures to radiations (Drs. O. A. TROWELL and D. R. LUCAS). It has proved possible to keep alive for periods of a week or so isolated "organs" of varying radiosensitivity such as retina and lymphoid tissue, without cellular multiplication. These cultures are exposed to radiation and the effect is judged by estimating the proportion of cells killed. With this preparation the adjuvant effect of, for instance, an atmosphere of oxygen can be assessed, a question of potential importance to the radiotherapist. Drs. R. H. MOLE and E. V. HULSE are studying

(*Continued at foot of next column*)

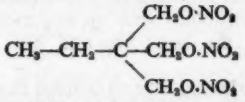
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Propatylnitrate

"Gina" (Bayer Products). Other names: ETTN. Etrynite. Ettriol trinitrate.

Chemistry.—An alkyl nitrate, 2-ethyl-2-hydroxymethyl-propan-1:3 diol, trinitric acid ester.



Dosage.—Supplied as 10-mg. white uncoated tablets. One tablet is taken sublingually or chewed for the acute attack, or half a tablet if side-effects (headache, nausea, palpitations) are marked. One tablet is swallowed three times a day for the prevention of attacks.

Properties and Therapeutic Uses.—This drug has been produced for the treatment of anginal pain by coronary vasodilatation, and it is claimed to be at least as effective as glyceryl trinitrate in the rapid relief of pain. In addition it is said by the manufacturers to have fewer and less severe side-effects and to have a longer action than glyceryl trinitrate.

In 1960 P. Nordqvist and E. Varnauskas[1] studied the effect of 10 mg. of the drug on acute attacks of angina in 44 patients: 20 considered it to be equivalent in effectiveness to glyceryl trinitrate, 13 preferred trinitrate, and 11 preferred gina. These workers gave the drug to a further 21 patients, 10 mg. b.d. or t.d.s., in an attempt to prevent acute attacks. It was thought to reduce the frequency of such attacks, and each dose seemed to work for about five hours.

In 1961 E. Sowton and S. Oram[2] produced an excellent and properly controlled study from King's College Hospital, London. They confirmed that the drug was as effective as trinitrate in the treatment of acute angina. Side-effects occurred in only 15%, and were equally common with gina and glyceryl trinitrate. No evidence emerged from the spontaneous comments of patients that gina acted for a longer time than trinitrate.

Comment.—New drugs for the treatment of angina appear rather frequently, and they rarely stand the test of time. On the evidence at present available propatylnitrate has no obvious advantage over glyceryl trinitrate, with the possible exception that the rare patient who has severe side-effects with trinitrate may be better off with propatylnitrate.

N.H.S. Basic Price.—100 tabs., 10 mg., 10s. 10d.

REFERENCES

[1] Nordqvist, P., and Varnauskas, E., *Svenska Läk.-Tidn.*, 1960, **30**, 2173.
[2] Sowton, E., and Oram, S., *Brit. med. J.*, 1961, **1**, 794.

(*Continued from preceding column*)

the effects of beta particles on the skin of mice, the incidence of tumours being correlated with factors such as radiation dose, fractionation of dose, etc. Another section is working on the treatment of lethally irradiated mice by grafts of marrow and lymphoid tissue. They find that not all "secondary disease"—the delayed reaction after such grafts—can be ascribed to immunological reactions of graft against host. The chemistry section under Mr. J. ST. L. PHILPOT is investigating various chemical "protectors." In some of this work it has been necessary as a preliminary stage to isolate the nuclei of cells by a new type of air-borne centrifuge. Another study, this time by the biophysics section, is that of the chronic radiation hazard from fast neutrons. This knowledge could assist our appreciation of what may happen in a nuclear reactor accident.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Corticosteroids in Asthma

SIR,—Many asthmatics who keep well on small (5 to 10 mg.) doses of prednisone find minor side-effects a small price to pay for their greatly increased health. Your leader-writer's strictures (November 25, p. 1413) on continuing corticoids were so dogmatic that I must point out what the facts are and how they can be interpreted.

Continuous corticoids are so helpful in severe asthma that once they have been given patients are loth to do without them. One interpretation of this fact is: "Corticoid treatment must not be given for long, because of the formidable problem of weaning patients from it"; but another way of saying this is: "Corticoids are often indispensable in managing asthma."

Some people believe in dispensing with corticoids in asthma. I believe in dispensing them.—I am, etc.,

London W.1. RICHARD ASHER.

SIR,—The communication by Dr. J. P. Knowles (November 25, p. 1396) on difficulties of weaning in steroid treatment of asthma draws attention once more to our misuse of the potent drugs with which the chemists continue to supply us. The steroid group has a profound effect on a variety of tissues. In addition to their valuable action in relieving bronchospasm they exert their effects on many other organs, but these actions are not needed in the treatment of asthma, and they may therefore be regarded as side-effects, which are sometimes disagreeable and occasionally dangerous.

Most physicians would agree that the steroids exert a powerful effect in status asthmaticus, and in cases of long-continued spasm which prove to be resistant to other forms of treatment. They act quickly as a rule, and the asthma should become responsive to treatment by simpler measures within a week, or ten days at the most. There is never any difficulty in weaning the patient at this point, and in the majority of cases this is the stage at which some other method of treatment should be substituted. Each case of asthma presents individual problems, and each needs treatment designed to counteract the factors which are found to be present. It may be assumed that most of the patients had been investigated before the emergency occurred, and the results should be sufficient to indicate which lines of treatment are most suitable.

Long-term steroid therapy can only be justified if the physician is convinced that there is no alternative. It is not merely a convenient substitute for other, and perhaps more tedious, measures. As it is sometimes used it appears to be an admission of therapeutic impotence.—I am, etc.,

London N.W.1. JAMES MAXWELL.

SIR,—The excellent article by Dr. J. P. Knowles (November 25, p. 1396) draws attention to the difficulty in withdrawing cortisone or one of its analogues in chronic asthma. The same can be said of any chronic disease treated by steroid suppression. To date the dangers and difficulties of the "withdrawal" syndrome have been seen most frequently in the long-term steroid treatment of rheumatoid arthritis. The same ugly compound of resurgent disease, adrenal exhaustion, and mental frustration is seen in any chronic disease when steroids are withdrawn too abruptly. In addition, fresh features of the suppressed disease may become evident; for instance, in rheumatoid arthritis, polyarteritic and neuropathic features. We would therefore gently take issue with your leader writer (November 25, p. 1413) when he says that the 12-day supply of tablets to an outpatient with asthma must be allowed to run out at the end of this period. While it may be highly desirable that the 12-day course of cortisone stops at this point, the physician may well find himself called from his bed during the next 48 hours to deal with severe status asthmaticus.

Dr. Knowles makes the point clearly that if the physician takes up steroid therapy to treat chronic disease he may never be able to lay it aside again.—We are, etc.,

Westminster Hospital, London S.W.1. F. DUDLEY HART. PETER EMERSON.

Chronic Bronchitis

SIR,—I agree with your opinion stated in the leading article on chronic bronchitis (October 14, p. 1004) that only a few patients with this condition benefit from corticosteroids. Perhaps even these should be reclassified as suffering from chronic asthma.

On the other hand there is a group in whom I find steroids frequently of the greatest value. These patients have not previously been subject to asthma or wheezy bronchitis, but, following an attack of acute bronchitis when the infection has been cleared by antibiotics or natural resistance, they continue to wheeze and to cough up mucoid sputum. Tests of ventilatory capacity at this stage show severe reduction. A short, sharp course of corticosteroids for two or three weeks combined with antibiotics for safety's sake, for the first week at least, usually produces a dramatic improvement with resolution of all the signs and symptoms of bronchial irritability and hypersecretion, and a return to a more normal level of ventilatory capacity. It seems probable that given at this stage steroids may help to break the vicious circle leading to chronic bronchitis or asthma.—I am, etc.,

City Hospital, York. W. H. HELM.

Pneumocystis Pneumonia

SIR,—In their article on pneumocystis pneumonia (November 18, p. 1327) Dr. W. F. White and his colleagues implicated long-term corticosteroid therapy as the main factor in predisposing adults to infection with *Pneumocystis carinii*, and suggested that long-term antibiotic therapy, the administration of cytotoxic drugs, and radiotherapy might play a part. We feel, too, that malignant disease of the reticulo-endothelial system combines in some peculiar way with long-term steroids in providing a suitable climate for the development of this infection, for it is surely more than coincidence that 10 of the 21 reported cases have suffered from such disease. To underline this point and support Dr. White's contention that the condition may not be so rare as the literature suggests, we would like to describe a further case, similar to their Cases 2 and 3, seen recently in this hospital.

A man aged 29 was discovered by mass radiography in July, 1955, to have enlargement of the glands at the right hilum, thought to be part of a tuberculous primary complex. He was completely symptom-free, and defaulted from follow-up. In February, 1959, he presented again, now with enlarged cervical, mediastinal, and inguinal glands, and a palpable spleen. A lymph-node biopsy showed typical Hodgkin's disease and he was treated with radiotherapy to the neck and mediastinum. This was repeated for a relapse in April, 1960, and at other times he received courses of nitrogen mustard (30 mg. on three occasions) and cyclophosphamide (a total of 15 g. orally over three months) and prednisolone in a dosage varying from 15 to 45 mg. daily from August, 1960, until his death in October, 1961.

The terminal illness commenced in July, 1961, with a relapse of the Hodgkin's process at all sites, severe hypoplastic anaemia, increasing dyspnoea with cyanosis, lassitude, and loss of weight. Chest *x*-rays then showed for the first time a "hilar flare" into both upper and mid zones of patchy fine-grain consolidation which was mistaken for Hodgkin's disease of the lungs. The shadowing gradually extended as his condition deteriorated, but he was not given any antibiotic therapy. The serum globulins were not investigated.

Post-mortem examination and microscopy of sections from selected representative tissues confirmed Hodgkin's disease, with transition to Hodgkin's sarcoma, in lymph nodes, spleen, and bone marrow but not in the lungs. *Post mortem* both lungs were bulky, solid with a soft rubbery feel, and showed uniformly greyish-white cut surfaces. Microscopically the lungs presented the characteristic "honeycomb" filling of the alveoli described in pneumocystis pneumonia. Of the large number of special stains used to demonstrate pneumocystis we found Leishman-Giemsa best for the vegetative forms, while Gram-Weigert gave most detail of the cysts, with hexamine silver next best. There was no evidence of Hodgkin's disease, cytomegalic inclusions, pulmonary oedema, or significant interstitial or plasma-cell pneumonia.

Unfortunately the diagnosis did not occur to us at the post-mortem examination and therefore no fresh tissue was available for direct smears, wet preparations, or animal inoculations. Considering these findings with the case history, it is evident that the progressive lung lesions discovered four months before death were due to pneumocystis pneumonia and that this was responsible at least in part for the excessive breathlessness from which the patient suffered during his terminal illness.—We are, etc.,

E. N. MOYES.
F. KURREIN.

Royal Infirmary, Worcester.

Photodermatitis from Soaps

SIR,—Professor C. D. Calnan and Drs. R. R. M. Harman and G. C. Wells (November 11, p. 1266) must be thanked for bringing to our notice the recent outbreak of photodermatitis from soaps.

I was pleased to learn of the co-operation of the soap manufacturers, but wondered why the names of the offending soaps were not mentioned. It is useless for the doctor to ask the patient if he is using a soap which contains tetrachlorosalicylanilide. It would be much easier if we could ask, for example, "Do you use Lifebuoy, Breeze, or what?" Perhaps we can be informed as to which products we are to suspect.—I am, etc.,

K. M. TOMLINSON.

Newent, Glos.

*** We referred this letter to the authors of the article, who write as follows: "The soaps which did contain tetrachlorosalicylanilide, from which we saw most of the cases of contact dermatitis, were Breeze and Lifebuoy toilet. However, it is understood that this substance was contained in a number of other soaps, as well as toilet and cosmetic products. Tetrachlorosalicylanilide is no longer manufactured and we do not think it has been used in soaps in this country for more than a year now."—ED., *B.M.J.*

SIR,—In the very timely article on photodermatitis from soaps by Professor C. D. Calnan *et al.* (November 11, p. 1266), there was, in my view, an important omission.

As they stated, tetrachlorosalicylanilide was withdrawn from the soaps referred to, but it is now known that the manufacturers then substituted tribromosalicylanilide. This is of importance for two reasons: firstly because there is now evidence that this substance also is a photosensitizer and contact-sensitizer and, what is far more important, that cross-sensitivity is known to exist between this and tetrachlorosalicylanilide. Many doctors may assume that because tetrachlorosalicylanilide was withdrawn in October, 1960, these soaps are now safe to use on tetrachlorosalicylanilide-sensitive patients, and it is important that they should know that this is not the case.

In conclusion, it would seem reasonable to regard any halogenated salicylanilide as a potential skin hazard until proved otherwise, for in my own series of cases there has been so far one instance of cross-sensitivity between both the above-mentioned substances and trichlorosalicylanilide. I think it should be known, if this letter and Professor Calnan's article are not to be meaningless, that these soaps are those which go by the names of Lifebuoy and Breeze.—I am, etc.,

K. D. CROW.

Princess Margaret Hospital, Swindon.

Oral Poliomyelitis Vaccine

SIR,—Your readers may be interested in knowing what has happened in Cincinnati, Ohio, since the intensive programme was initiated in the spring of 1960 using the oral anti-poliomyelitis vaccine. In 1960 a total of 187,650 of the Cincinnati population of 500,000 received the vaccine. (Three types in three separate doses.) These were children between 3 months of age and 18 years. The programme began in April, 1960, and finished in January, 1961. In the spring of 1961 infants and pre-school children who had not received the vaccine were offered it and approximately 18,000 were so protected. By this means an order of 75% of the children of the city were protected. Surveillance for possible cases of poliomyelitis in the city was maintained in 1960 by Dr. A. Sabin, and in 1961 by the City Health Department in collaboration with the hospitals and the State Public Health Laboratory. In 1960 "one case of poliomyelitis was reported, but onset of paralysis occurred 13 days after the patient, a 25-year-old man, returned to this area from an extended stay in another part of the United States. He had received neither Salk nor Sabin vaccine, and he was never associated with any child who had received the Sabin vaccine. One case resembling paralytic poliomyelitis was reported in Hamilton County (in which Cincinnati is the major city) in September, 1960. This case was investigated, but Dr. Sabin and his staff who were doing the follow-up during 1960 were unable to isolate any poliovirus or to demonstrate any rise in titre of poliomyelitis antibodies. They did isolate and demonstrated infection with an E.C.H.O. type 6 virus."[1]

During 1961 the Cincinnati Health Department carried out a meticulous follow-up of all suspected cases and the results proved exceedingly interesting. The findings up to October 15, 1961, are as follows: Thirty-two patients suffering from poliomyelitis-simulating diseases were studied. One case was admitted to a Cincinnati hospital from a neighbouring county (Clermont) with clinical symptoms resembling poliomyelitis, but the diagnosis was not supported by positive laboratory findings. Another case from outside the city was admitted to a Cincinnati hospital and poliovirus type III was isolated from a stool of this patient. Up to the time of writing—November 24, 1961—there has been no evidence of poliomyelitis in Cincinnati itself.

Of the 32 cases, 20 were cases of aseptic meningitis so-called, and specimens from these cases were studied in the laboratory. The following is a breakdown of the organisms so far identified: polio type III, 1; Coxsackie B5, 6; E.C.H.O. 9, 5; E.C.H.O. 18, 1; mumps, 2; and leptospirosis (?), 1. A full report of this surveillance period is being prepared for publication, with full laboratory details and case material.

We are satisfied that no actual poliomyelitis occurred in Cincinnati during the period April, 1960, to October, 1961, which can be conclusively shown to have arisen in Cincinnati itself. The cases that were admitted to Cincinnati hospitals were from the county areas, or were infected outside the city. We are satisfied also and agree with your editorial comment that "oral poliomyelitis vaccine offers the greatest possibility of completely eliminating poliovirus as a human pathogen provided proper safeguards are taken in its manufacture and careful surveillance of the community is maintained" (October 21, p. 1072). Incidentally, in the two years during which the Sabin oral vaccine has been used in Cincinnati there has been no serious reaction reported of any kind.—We are, etc.,

KENNETH I. E. MACLEOD.
Board of Health, Cincinnati, Ohio, U.S.A. T. AIDAN COCKBURN.

REFERENCE

1 Porter, E. R., and Wehr, R. E., *Publ. Hlth Rep. (Wash.)*, 1961, **76**, 369.

Human Orf

SIR,—Drs. J. Nagington and C. Howard Whittle (November 18, p. 1324) mention that transmission of orf from person to person has not been recorded. I regret to say that it has, however, taken place accidentally.

About five years ago I excised, with my only pair of stitch scissors, the sodden skin around the base of a typical necrotic papule on the finger of a shepherd, who admitted having orf in his flock. The next patient was a lad of about 18 years, for removal of stitches from his cheek, after excision of a small sebaceous cyst a few days previously. The scissors were rapidly cleaned with surgical spirit instead of being re-boiled, and the stitches removed. During this he was slightly jagged with the point of the scissors. Two or three weeks later this lad came back with a characteristic orf lesion on his face, on the scar-line where he had been jagged. It ran the usual course.

Had I then known that person-to-person transmission had not been recorded, the exact details of incubation time would have been taken. But orf is not highly rare to general practitioners in this area. I have seen six or seven cases in the last twelve years, and of course none needed sending to hospital. Not all shepherds who contract it even consult a doctor. Several morals are painfully obvious.—I am, etc.,

Newton Stewart, Wigtownshire. H. A. LANG.

"Albustix": False-positive Reactions

SIR,—It has been brought to our attention by Dr. D. McColl, medical officer of the Nobel Division of I.C.I., that the presence of a small amount of "savlon" hospital concentrate (15% cetrimide and 1.5% chlorhexidine) in either urine or water causes "albustix" reagent strips to give a positive reaction, whether protein is present or not. We have confirmed this finding and have shown that at concentrations above 1 in 20,000 a false positive reaction is given by cetrimide, benzalkonium chloride, chlorhexidine, also by dodecyl di-(aminoethyl) glycine hydrochloride ("Tego" 103S), and other ampholytic surface-active agents. Anionic compounds on the other hand, such as the common phenols, soap, sodium lauryl sulphate, and dodecyl benzene sulphonate, are without effect in low concentrations.

Albustix reagent strips are impregnated with citrate buffer to *p*H 3 and contain tetrabromophenol blue indicator. The latter is known to form complexes with both quaternary ammonium compounds and chlorhexidine, and no doubt this explains the false-positive reaction. Receptacles that have been cleaned and/or disinfected with any of the materials already mentioned should therefore be rinsed well with water before being used for urine samples. The Ames Company, manufacturers of albustix, state that their literature warns that disinfectants, particularly those containing quaternary ammonium compounds, may affect the albustix reaction.—I am, etc.,

I.C.I. Limited, Pharmaceuticals Division, Wilmslow, Cheshire. R. HALL.

Test-papers for Plasma Pseudocholinesterase

SIR,—In general I agree with the statements made by Drs. H. C. Churchill-Davidson and W. J. Griffiths (October 14, p. 994) for the usefulness of the test-paper method for the determination of plasma pseudocholinesterase activity. However I would like to point out to the authors that temperature correction is an important factor even for clinical accuracy. As pointed out by Dr. R. Richterich,[1] to correct values for 20° C. the factor is 1.11 at 18° C. and 0.8 at 25° C.

Further, out of our own series of 192 healthy blood donors we found in 165 individuals normal activity with an endpoint at 5–20 minutes (according to the manufacturers of "acholest"). However, 27 persons (14%) showed values of 20.5–33 minutes—that is, decreased activity. From a footnote of the paper under discussion it becomes clear that normal values were different in two batches of test-paper. This observation together with our results in normal individuals make one question the stability of the substrate on the paper. It seems necessary to delineate under controlled temperature conditions the normal range for this promising enzyme paper-test before it gets too early into the hands of the practitioner.—I am, etc.,

Medizinische Universitäts Poliklinik, Basle, Switzerland. ULRICH C. DUBACH.

REFERENCE

1 Richterich, R., *Bull. schweiz. Verein. klin. Chem.*, 1961, **2**, 29.

Mixing Solutions in the Theatre

SIR,—A surprising number of fatalities occur during local analgesia as a result of wrong solutions being injected or applied topically.

As has been made apparent by recent letters to the *B.M.J.*, most variants of local agents and haemostatics are available sterile and ready for use. It is a matter of surprise to me that for operations when not more than 10 ml. of solution is needed a dental syringe using a cartridge is not more generally employed. The dental syringe is a most convenient and economical piece of apparatus. The needles are first class and inexpensive, and in addition cartridges are available of all varieties of analgesic drugs and different strengths of haemostatics. The dental syringe takes little time to prepare and its use would be found to be a matter of great convenience in ear, nose, and throat work, as well as in the out-patient department of busy hospitals.

Most plastic surgeons use such syringes, and a number of ear, nose, and throat surgeons that I know would never use any other method for injecting a local. I contend that the use of such a syringe with prepared solutions in cartridges would decrease considerably the risk of overdosage or the injection of wrong solutions.—I am, etc.,

London W.1 VICTOR GOLDMAN.

Renal Tubular Acidosis

SIR,—Your annotation on this subject (November 11, p. 1276) contains several inaccuracies. You state that Lightwood just described the infantile form of the disease, yet his brief report of "Calcium infarction of the kidneys in infants"[1] made no mention of the metabolic abnormalities by which the disease is now recognized, and could equally well have referred to idiopathic hypercalcaemia, a syndrome which has since become associated with his name. In the following year Butler, Wilson, and Farber[2] (whose work you failed to mention) published the first clearly recognizable description of renal tubular acidosis, in which they emphasized the presence of acidosis and hyperchloraemia, and recounted unsuccessful attempts at treatment with alkalis. Their paper also included the first account of the late childhood or adult form of the syndrome, which is usually associated with the name of Albright. One of these patients was a man aged 20 who had recently had a parathyroid tumour removed. The previous hyperparathyroidism of this patient was probably not unrelated to his tubular acidosis, for it is now recognized that a number of hypercalcaemic disorders can give rise to urinary acidification defects.[3,4]

In your final sentence you state that "simple therapy with an alkaline mixture will prevent the serious effects of osteomalacia, nephrocalcinosis, and hypokalaemia." These hazards are not invariable complications of the untreated disease, and so in any patient it is impossible to be sure that treatment has prevented their appearance. But there is no definite evidence that treatment with alkalis alone will cure these complications once they are present. No single instance of osteomalacia cured by alkalis alone has been reported, for vitamin D has always been given as well. Vitamin D will cure osteomalacia in other forms of renal disease, whether acidosis is present or not,[5,6] and it is quite possible that vitamin D, and not the alkalis given simultaneously, has been responsible for the healing of the bones in tubular acidosis. Similarly there is no published evidence that alkalis, unless given in the potassium form, will lessen the risk of potassium depletion. Nephrocalcinosis has been shown to lessen with treatment on three occasions,[7-9] but usually improves little if at all, and may progress further.

Your reviewer clearly takes Albright's view[7]—although fortunately not his terminology—that most of the features of renal tubular acidosis are due to deficiencies of "fixed base" (i.e., the cations sodium, potassium, and calcium) which the kidney must excrete in company with "fixed acid" (the anions chloride, phosphate, and sulphate) because it cannot excrete a sufficiently acid urine. Most workers in this field do not now consider that osteomalacia, nephrocalcinosis, or potassium deficiency are entirely the result of the acidification defect or the consequent acidosis. All these faults, and the failure to form a concentrated urine which is an almost invariable feature of the syndrome, are more likely to be direct effects of a biochemical error involving a sharply defined length of renal tubule. Acidosis is usually the first metabolic consequence to declare itself, but may be preceded by nephrocalcinosis,[3] or rarely by potassium deficiency with an associated alkalosis.[10]—I am, etc.,

Department of Medicine, Postgraduate Medical School, London W.12. OLIVER WRONG.

REFERENCES

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2. Butler, A. M., Wilson, J. L., and Farber, S., *J. Pediat.*, 1936, **8**, 489.
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4. Fourman, P., McConkey, B., and Smith, J. W. G., *Lancet*, 1960, **1**, 619.
5. Stanbury, S. W., *Brit. med. Bull.*, 1957, **13**, 57.
6. Dent, C. E., Harper, C. M., and Philpot, G. R., *Quart. J. Med.*, 1961, **30**, 1.
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Hypothyroidism in the Elderly

SIR,—The interesting paper by Drs. W. H. Lloyd and I. J. L. Goldberg on the incidence of hypothyroidism in the elderly (November 11, p. 1256) draws attention to one of the more difficult problems in clinical medicine, that of distinguishing between the changes due to hypothyroidism and those due to old age. The striking absence of correlation between the various investigations undertaken by the authors (their Fig. 1) underlines this difficulty, and it is evident that the diagnostic criteria in hypothyroidism are by no means clear-cut.

My experience of elderly patients in recent years approximates numerically with that of Drs. Lloyd and Goldberg, and I agree that hypothyroidism in the elderly is usually a severe illness, which carries a high mortality rate due to delay in diagnosis, the development of cardiac and mental complications, and the occurrence of hypothermic coma. I am surprised, however, at the high incidence claimed for this disease, since 58 cases in 2½ years must represent on the average one new case every two to three weeks. My own experience does not support such a high incidence for hypothyroidism in elderly patients.—I am, etc.,

Brighton Geriatric Unit, Brighton General Hospital, Brighton 7. A. M. CANTOR.

Thiazide Diuretics and Diabetes Insipidus

SIR,—We cannot agree with some of the comments in your annotation on thiazide diuretics and diabetes insipidus (November 18, p. 1344). It is not true to state that other diuretics do not check the polyuria in this disease. Mersalyl was observed to reduce urine volume in diabetes insipidus as long ago as 1924,[1] and we have confirmed this. A similar effect may follow the administration of spironolactone. With both these drugs the effect was delayed 24 hours and was dependent upon electrolyte loss; thus acute experiments will not reveal the antidiuretic action.

We have investigated the effects of diuretic therapy on renal water excretion in eight patients with vasopressin-insufficiency diabetes insipidus.[2] We have found that treatment with the thiazides was followed constantly by a marked fall in glomerular filtration rate. This effect was immediate and preceded significant electrolyte loss; it may be accounted for by a direct action on the renal vasculature. Following the induced salt excretion a further fall in glomerular filtration rate occurred, and this appeared to be similar to the effect produced by mersalyl and spironolactone.

We believe that the fall in glomerular filtration rate determines the reduction in urine flow. This may be explained by the fact that a reduction in glomerular filtration rate would also diminish the sodium filtered through the glomerulus. In consequence the concentration of sodium would be increased in the peritubular vessels and hence, also, in the renal extracellular fluid in the region of water reabsorption. This would enhance the osmotic gradient across the distal tubular membrane and would in turn lead to increased reabsorption of water.—We are, etc.,

St. Bartholomew's Hospital, London E.C.1. C. W. H. HAVARD.
Postgraduate Medical School, London W.12. PHILIP H. N. WOOD.

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[2] Havard, C. W. H., and Wood, P. H. N., *Clin. Sci.*, in press.

Acute Myxoedema

SIR,—Dr. R. E. Kendell's severe criticisms (November 11, p. 1289) of our paper (October 21, p. 1063) fall into two contradictory parts: (*a*) our patients did not have myxoedema; (*b*) the myxoedema was not of acute onset.

Dr. Kendell apparently bases the diagnosis of myxoedema on radio-iodine tests and the basic metabolic rate, but the one thing he seems to forget is to look at the patients. All our five cases had severe myxoedema which could be diagnosed on sight; three of the five patients were in coma, and two of them died within 12 hours and four days respectively, the diagnosis in both cases being confirmed at necropsy. The other three patients had typical E.C.G. tracings, raised serum cholesterol (>300 mg.), radiological evidence of cardiac enlargement, radio-iodine uptake consistent with hypothyroidism (two cases), and an unmistakable response to thyroxine with reversion of the abnormal changes. Our critic does not find this sufficient evidence of "significant hypothyroidism."

His second argument is that we have not proved that the patients were "originally euthyroid." Such proof is clearly impracticable and we have naturally depended (as pointed out in the paper) on the clinical history, corroborated where possible by relatives and family doctor. The evidence varied in strength from case to case, but Dr. Kendell is not justified in treating with contempt statements that "a man of 60 was well and working until three days before admission," or that a woman of 73, closely observed by her family doctor, was seen to be "pretty alert and active" until myxoedema with coma developed over a period of 48 hours.

Above all, he chooses to misrepresent the basic meaning of our paper. We have not assumed—as he implies—that these patients' thyroid glands were previously normal, and in fact we have adduced clinical and experimental evidence to show that this was most unlikely. We quote: "It is our hypothesis that in the five cases reported by us the thyroid gland was already considerably damaged, and that the residue of functioning thyroid tissue was working under maximum stimulation from the thyrotropic hormone. There was therefore no clinical hypothyroidism prior to the onset of the acute illness (with the possible exception of Case 2), but these patients had no reserve when exposed to severe stress."

Finally, he makes great play of our statement that "search of the literature has not produced any well-substantiated cases of acute myxoedema." It was precisely the purpose of our paper to draw attention to a condition which we believe exists but is apparently not recognized. It may not be out of place to point out that the 1948 edition of Means's *The Thyroid and its Diseases*[1] contained no hint of myxoedema coma, first described in London 60 years earlier but unrecognized until 1953, since when cases have been reported from many parts of the world.—We are, etc.,

Reading, Berks. W. HAUSMANN. A. J. KARLISH.

REFERENCE

[1] Means, J. H., *The Thyroid and its Diseases*, 1948, 2nd edition. Lippincott, Philadelphia.

Traumatic Rupture of the Heart

SIR,—The report of a case of rupture of the heart by Dr. W. W. Deacon (October 21, p. 1067) and the letter on the same subject by Dr. C. R. Tribe (November 11, p. 1289) have great interest for those engaged in traumatology. Though crush injuries to the chest are common, rupture of the heart and great vessels is rare.

The essentials of the post-mortem report on the patient described by Dr. Deacon seem to be the fracture of seven ribs on the left side anteriorly, much bruising of the heart wall, and a rupture of the heart at the tip of the right ventricle. This evidence strongly suggests that the heart was crushed between the thoracic cage and the spinal column. The ventricle would be more likely to split at the moment of impact if it were filled with blood. The left ventricle may be more protected from such trauma. It seems possible that a similar mechanism obtained in the case described by Dr. Tribe, but no extensive bruising of the heart is recorded and there is no evidence of injury to the thoracic cage. However, it seems to me that there are other mechanisms involved and such mechanisms have interested me for some years during the preparation of a work on some aspects of traumatology.

There is general agreement that haemothorax can occur in a chest injury without there being any overt injury to the thoracic cage. Haemothorax is not necessarily associated with fractured ribs therefore, acute distortion being sufficient to cause the rupture of vascular tissue. Rapid deceleration, whether in a

vertical or horizontal direction, will produce shearing stresses on the organs and tissues, and rupture of the aorta has been discussed by Parmley[1] from this point of view. It would appear that the aortic arch may fail to restrain the momentum of the weighty heart and a transverse tear of the aorta results. There seems little doubt that such transverse tears occur by a shearing mechanism.

If acute tension is applied to an elastic tube beyond the elastic limit a transverse tear will result. Such a happening is not unknown in the oesophagus in the acts of vomiting or the lifting of heavy weights. More commonly, it seems to me, tubular structures may be subjected to an acute rise of pressure from within the lumen, resulting in a longitudinal split of the wall. There is a ready simile with the frozen water pipe where a sudden expansion from within causes a longitudinal crack in the wall of the pipe. If the oesophagus is on the stretch and a quantum of stomach content is forced into it, as in vomiting, the acute rise in intraluminal pressure may be sufficient to rupture the lower end of the oesophagus, a longitudinal tear resulting. This seems to be the commonest type of rupture of the lower end of the oesophagus.

Within recent years there came under my care a lad who had sustained a crush injury to the lower chest region. Shock was severe and only a temporary improvement was obtained with resuscitative measures. The post-mortem examination revealed a longitudinal split in the arch of the aorta. It seemed clear that the violence to the aortic arch was not direct. Though the aorta can withstand pressures of the order of 2,000 mm. Hg, acute pulse-like pressures can be very destructive. In this instance it seems highly probable that the aorta overlying the upper lumbar spine was acutely compressed, resulting in a pulse of high intraluminal pressure which ruptured the aortic arch. Under similar mechanical circumstances, if the aortic valve were open at the moment of impact a split in the left ventricle could result.—I am, etc.,

Wembley Hospital, Wembley, Middlesex. J. S. CALLCUTT.

REFERENCE

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Economical Use of Nursing Ability

SIR,—I am surprised that Dr. W. N. Leak (November 25, p. 1429) blames the medical profession for current difficulties experienced by the nursing profession, for doctors can never have felt so much excluded from responsibility for nurse training as they do at the present time. There seems to be a progressive worsening of the standard of personal care of the sick patient in hospitals. A main reason for this may well be a refusal by the General Nursing Council or the Royal College of Nursing to recognize that the personal care of the patients should be a *first* responsibility of the student nurse. Her first loyalty should surely be to the ward—not to the lecture theatre as at present. The *esprit de corps* of the ward unit which we admired so much 30 years ago has been undermined by the current emphasis on the lecture theatre.

My solution to the nursing problem is to introduce legislation which would ensure a majority of hospital doctors on the General Nursing Council (male or female), and to try and get back to the successful training principles of 30 years ago. These may have been hard physically but they were psychologically satisfying to the probationer. The patients were well cared for, the wards were clean, and the ward sisters had a fine sense of achievement.—I am, etc.,

Oxford. W. RITCHIE RUSSELL.

V.D. Examinations in Prison

SIR,—In reply to Dr. Maria Leigh's letter entitled "V.D. examinations in prisons" (November 25, p. 1431), I should like to start by answering her last question first and say that I only wish that a cut-and-dried category could be established of "the person unlikely to suffer from V.D." It would make the work of all venereologists, particularly those who also do routine examinations of a community, very simple.

Women prisoners have equal rights with their more fortunate sisters outside in being able to refuse examination or tests of any kind, and the "old lag" has the same right of refusal as the "star"—that is, a woman convicted for the first time. No woman, whether convicted or even on remand with a request from court for V.D. tests, is subjected to tests without consent.

The "Clinic" of H.M. Prison, Holloway, also deals with all minor gynaecological complaints far more than in any other special clinic; from menopausal disorders to non-venereal discharges. It is well known that *Trichomonas vaginalis* has no respect for status, "star" or strumpet. A convicted woman seen for the first time is not asked to have "swabs" taken unless there is an indication for such an examination either from her mode of life or unless the woman complains of some disorder.

I presume that Dr. Leigh's letter refers to a recent incident. I have therefore examined my records for the last three months and find that, of the women convicted for atom-bomb demonstrating, only one was examined and had "swabs" taken and then only because she complained of certain symptoms. She did not object to examination, which, in the event, revealed no signs of any abnormality of any kind.—I am, etc.,

London N.7. ELIZABETH KEIGHLEY, Consultant Venereologist in Charge, Special Clinic, H.M. Prison, Holloway.

SIR,—I should like to suggest to Dr. Maria Leigh (November 25, p. 1431) that it is a dangerous practice to assume that a "Ban the H-Bomb" marcher is "unlikely" to suffer from V.D. It is a fact that V.D. occurs in every class, profession, and trade in our society, much more frequently than many imagine, as the victim of this "unlikely" assumption has often found to his or her cost.

Whether a routine examination of prisoners for V.D. should be obligatory is a matter for discussion, but I am strongly of the opinion that all immigrants into this country should be tested or produce a medical certificate of freedom from V.D., if such a procedure is practicable, and that we should discard all ideas of "likely" or "unlikely" with regard to any particular class or individual.—I am, etc.,

Snitterfield, Warwicks. ERIC ASSINDER.

Phenylbutazone and Leukaemia

SIR,—Following Dr. R. H. D. Bean's report of six cases of leukaemia associated with recent phenylbutazone therapy,[1] there have appeared in these columns two further cases of leukaemoid reactions

following phenylbutazone administration (Dr. A. Lawrence, December 10, 1960, p. 1736, and Dr. J. V. Garrett, January 7, 1961, p. 53). In addition, Dr. R. Scheurer-Karpin (March 18, 1961, p. 823) draws attention to similar experiences with analgesics containing an aminophenazone derivative, including phenylbutazone. I wish to record a further case of leukaemia associated with prolonged phenylbutazone therapy.

The patient, aged 59, was first seen at University College Hospital in 1951 complaining of "rheumatism" in her hands. Rheumatoid arthritis was diagnosed and she was treated symptomatically. Her Hb was 100% and E.S.R. 10 mm. at this time. Over the next eight years she was seen at varying intervals because of progressive osteoarthritis of the right hip. Routine analgesics provided little relief and phenylbutazone, 100 mg. t.d.s., was started in June, 1959. After two months she developed nausea and vomiting which cleared on temporary cessation of phenylbutazone. From September, 1959, until September, 1960, she took phenylbutazone, 100 mg. t.d.s., uninterrupted by any apparent side-effects.

In September, 1960, her Hb was 89%, E.S.R. 11 mm., and W.B.C. 4,000 with a normal differential. The Rose-Waaler test was negative. A suppository form of phenylbutazone was substituted and surgery advised for her osteoarthritic hip. In November, 1960, she complained of swelling of her face accompanied by an urticarial rash of face, neck, and arms. Phenylbutazone was discontinued, with relief of her symptoms, and the patient took no more.

When admitted to hospital in January, 1961, she was found to have gross osteoarthritis of the right hip-joint and early rheumatoid arthritis in both hands. Her Hb was 82%, E.S.R. 26 mm., and *x*-rays demonstrated gross osteoarthritis of the hip-joint with degenerative changes in the lumbar spine. A subtrochanteric osteotomy was performed.

One week post-operatively she developed a high swinging temperature for which no cause was immediately obvious, but her Hb was 50% and W.B.C. was 58,400. Preliminary examination of the blood-film suggested a diagnosis of an acute leukaemia. Blood cultures, later to yield a proteus, and bone-marrow biopsies were taken, and the patient was started on chloramphenicol, 250 mg. q.d.s.; busulphan, 2 mg. q.d.s.; and intravenous 5% dextrose. The peripheral blood-film and bone-marrow morphology were atypical, but it was thought the most likely diagnosis was either chronic myeloid leukaemia or an acute monocytic leukaemia of the Naegeli type. The peripheral blood consisted mainly of peroxidase-positive myelocytes, and the bone-marrow was hyperplastic, composed mainly of immature cells without nucleoli and "blast" cells. Myelopoiesis was grossly abnormal, there was little erythropoiesis, but the megakaryocytes were increased in numbers, many containing numerous separate nuclei.

On the fourteenth post-operative day she became anuric and died in coma that same evening. *Post mortem* the overall picture was that of a chronic myeloid leukaemia. Histology showed that the vertebral bone-marrow was densely replaced by primitive cells resembling myelocytes or monocyte precursors. The liver and kidneys were heavily infiltrated with leukaemic cells.

It is recognized that blood dyscrasias are important and not uncommon complications of phenylbutazone therapy.[2-4] It is reasonable to suspect that phenylbutazone has some part to play in the causation of leukaemia when leukaemia, and leukaemoid reactions, develop on a number of occasions in patients who have received a recent prolonged course of phenylbutazone. This patient had received 210 g. of phenylbutazone, with two associated sensitivity reactions, in the 18 months before her death. It is concluded that there may be a strong possibility of a relationship between phenylbutazone therapy and leukaemia.

I wish to thank Dr. H. A. Burt and Mr. C. W. Flemming for permission to report this case, and Dr. T. A. J. Prankerd, who advised on the treatment of the leukaemia.

—I am, etc.,

General Hospital, Nottingham. I. P. CAST.

REFERENCES

1 Bean, R. H., *Brit. med. J.*, 1960, **2**, 1552.
2 Hale, G. S., and DeGruchy, G. C., *Med. J. Aust.*, 1960, 449.
3 Leonard, J. C., *Brit. med. J.*, 1953, **1**, 1311.
4 Mauer, E. F., *New Engl. J. Med.*, 1955, **253**, 404.

Neuropathy after Thalidomide ("Distaval")

SIR,—I reported (October 21, p. 1084) a case of neuropathy after prolonged treatment with "distaval" (thalidomide) in normal dosage in which amenorrhoea had also been present for eighteen of the twenty months the drug had been taken. It is interesting to note that seven weeks after stopping thalidomide a perfectly normal period came on. All the normal symptoms associated with the patient's past menstrual history were present. No hormones had been given to produce this period.

Neurological symptoms have not progressed any further since stopping distaval, but have not, unfortunately, regressed.—I am, etc.,

Nuneaton, Warwicks. PHILIP HOWE.

SIR,—I was interested in reading the comment in the article by Drs. Pamela M. Fullerton and Michael Kremer (September 30, p. 855), and alluded to in your leading article (p. 876), that glutethimide ("doriden"), which is chemically related to thalidomide ("distaval"), has not been reported to cause neuropathy. I have seen two cases of reversible peripheral neuritis that I am convinced were caused by the prolonged ingestion of glutethimide.

I have reported elsewhere[1] five cases of "acute on chronic" intoxication with glutethimide and one of these (Case No. 4) on follow-up demonstrated a classical picture of peripheral neuritis. This man had, over a period of some 18 months, been taking glutethimide intermittently. The dose varied considerably, but the average was 10–12 tablets per day (2.5–3 g.). He was first seen in an acutely intoxicated state as a result of taking 5 g. of the drug at one time. After a short period of abstinence he began taking between 8 and 10 (2–2.5 g.) of the tablets daily. When later seen he had a typical peripheral neuritis involving the legs. The clinical picture included bilateral paraesthesia, tenderness, diminished knee and absent ankle jerks, mild ataxia, and diminished appreciation of all types of sensation. The most impressive feature was a third-degree burn over the subcutaneous surface of the tibia of the right leg, which remained painless, sustained, without his immediate knowledge, in front of an electric fire. The drug was withdrawn, vitamin-B complex given parenterally, and over four months the legs returned to near normal.

The second case related to a female who took some six tablets (1.5 g.) daily for about nine months. She also had clinical signs and symptoms restricted to the lower limbs. The evidence for the peripheral neuritis was some weakness of both legs, a mild ataxia—"I feel unsteady, it's like walking on foam rubber"—diminished jerks, and sensory impairment involving all modalities. The condition improved with cessation of taking the drug and parenteral vitamin-B complex. After 10 weeks there was no evidence of ataxia and the patient felt more steady, the knee jerks were elicited, and sensory impairment was less marked.

No other cause could be ascertained for these cases of peripheral neuritis. No other drugs were being taken.

Alcohol was not taken in sufficient quantity to be indicted, and in any case the condition improved with the drinking habits remaining unchanged. It was thought worth recording these two cases in the light of the comment that such a condition has not been described before.—I am, etc.,

Fitzroy, N.6, Victoria, Australia. ALLEN A. BARTHOLOMEW.

REFERENCE

[1] Bartholomew, A. A., *Med. J. Aust.*, 1961, **2**, 51.

"Nervessa"

SIR,—I have followed with interest the recent correspondence in your columns on "Aspirin Anonymous," with particular reference to "alka-seltzer." I now learn with dismay that the drug firm marketing this product are launching a triple bromide preparation under the name of "nervessa." This American product consists of effervescent tablets each containing a total of 9.5 gr. (617 mg.) of bromide. The recommended dose is 1–2 tablets with a maximum of three in 24 hours. Nervessa is being widely advertised in the lay press, and no doubt will be sold in millions.

Bromides are excreted very slowly in the urine and are thus capable of producing cumulative effects. These chronic toxic effects ("bromism") include halogen acne, gastro-intestinal and neurological disturbances, and mental effects ranging from depression, lassitude, and faulty memory to acute psychosis with dementia. The earliest symptom of bromism may be excitement, and this may lead the user to the disastrous mistake of increasing the dose of the drug. Thus we may have a person taking the drug for relief of the very symptoms of bromide intoxication which they produce. The drug should be stopped in any person who develops even slight symptoms of mental confusion; abundant fluids and supplementary sodium chloride should be given.

Bromides have a limited use to the physician provided the patient is kept under constant surveillance. The profession, however, must strongly condemn the unrestricted sale of "nerve tonics" containing bromides over the chemists' counter to the general public.—I am, etc.,

London S.E.16. K. LANCER.

Intestinal Bleeding after Nitrofurantoin ("Furadantin")

SIR,—I wish to record the occurrence of intestinal bleeding following a course of "furadantin" (nitrofurantoin). The amount taken was 500 mg. daily for five days. Bleeding was first noticed two days after the course was completed and continued, macroscopically, for four days. The blood was clotted and intimately mixed with the faecal material, and appeared to have originated from the lower end of the small intestine. No other therapy was taken with the furadantin, but a course of "urolucosil" (sulphamethizole) had been taken a week previously. There is no history of previous intestinal bleeding.

Subsequent intravenous pyelography revealed a satisfactory condition of the kidney that had been infected, and a barium meal, followed by a barium enema, failed to demonstrate any lesion within the gastro-intestinal tract.

Since the makers of furadantin state that there have not been any other reports of bleeding from the intestinal tract following furadantin therapy, either in this country or in America, I should be interested to hear from anyone who has had a similar experience.—I am, etc.,

Birmingham 20. GILBERT R. SMITH.

Cytotoxic Drugs and Radiotherapy

SIR,—I have read with interest the letter from Mr. Anthony Green (October 21, p. 1085), and I agree wholeheartedly with what he has stated there. Many cytotoxic drugs could be included under the heading "antimitotics" or "radiomimetics," and from a fair experience of these drugs I think that most antimitotic drugs arrest the dividing cell, probably in the metaphase, or result in chromosome breaks and may render the cell vulnerable to the lethal agent; and the best lethal agent we have at the present moment is some form of radiotherapy.

There would appear to be no doubt that these antimitotic drugs are not competitors to radiotherapy, but rather that they act synergistically, and thus prepare the cell for the lethal blow. I think that malignant growths should be treated in the first instance by an antimitotic drug in order to prepare or sensitize the cell towards the radiotherapy that will follow, and even when radiotherapy has commenced I think the antimitotic drug should be continued until the course of treatment is over.—I am, etc.,

London W.1. R. CHRISTIE BROWN.

Carcinoma-in-situ

SIR,—An erratum is in order in reference to your *compte rendu* of the First International Congress of Exfoliative Cytology (October 7, p. 953). The correct figures pertaining to our study of *in-situ* carcinoma and related abnormalities are as follows: The total number of cases studied was well over 90 (not 70 as stated). Of these, 25% had progressed towards various forms of cancer, 50% remained stationary (not 25% as stated), and 25% disappeared (not 50% as stated). I sincerely hope that you will be able to place this clarification in your esteemed publication.—I am, etc.,

Memorial Hospital for Cancer and Allied Diseases, New York 21. LEOPOLD G. KOSS.

Causes of Bronchial Cancer

SIR,—Your leading article (October 28, p. 1134) recalls the work of Peyton Rous on rabbits, and draws attention to the recent work on a postulated pre-cancerous state of the bronchial mucosa of man. This work might be thought to support the very common assumption that chemically induced cancer of the skin in man is always preceded by a pre-cancerous condition.

It is true that by the time a man develops tar cancer (the only kind I am familiar with) he has very often developed other skin changes, such as patches of hyperkeratosis, telangiectases, and alterations in the skin texture. It does not follow, however, that these so-called pre-cancerous skin changes necessarily precede the development of skin cancer. Some years ago I reported[1] on a group of tar-workers, and showed that whereas the incidence of these various skin changes increases with the duration of exposure, as does the incidence of tar cancer, there were many cases of tar cancer in men

with few or none of the other changes. As it is now well recognized that tar molluscum is, in fact, a tar-induced molluscum sebaceum, and as molluscum sebaceum is well known to occur on otherwise normal skin, this need cause no surprise.

I call attention to this point because I know of some cases in which the absence of the so-called pre-cancerous changes resulted in a diagnosis of tar cancer being missed.—I am, etc.,

R. E. W. FISHER,
Chief Medical Officer,
South Eastern Gas Board.

London S.E.15.

REFERENCE

1 Fisher, R E. W., *A.M.A. Arch. industr. Hyg.*, 1953, 7, 12.

Smoking Cures

SIR,—The main problem in smoking addiction is the underlying motivation. This is frequently self-consciousness, lack of confidence, and the stresses and anxieties of the modern pattern of living. As these underlying factors will usually remain unaltered, it is only to be expected that many people will take up smoking again after a period of time, although their actual nicotine addiction may have been overcome. It is difficult to see how any drug or smoking cure can be expected to answer this problem.

It appears that the withdrawal symptoms that occur on attempting to give up the habit can be effectively controlled by temporary substitution of a drug such as lobeline (see *Brit. med. J.*, November 4, p. 1229). Such preparations may therefore be of value when there is a genuine wish to give up smoking or when this is important medically in chronic bronchitis and other conditions. It can be compared with appetite-suppressives, which may help in obesity by damping down the appetite until the patient has adjusted himself to a smaller food intake.—I am, etc.,

G. BARRY CARRUTHERS.

London W.1.

The Case of the Plastic Surgeons

SIR,—The British Association of Plastic Surgeons has taken notice of the observations of the president of the Disciplinary Committee of the General Medical Council on November 25 (*Supplement*, December 2, p. 223) with the respect which is due to the authoritative tribunal of all registered British medical practitioners.

Our colleagues of the medical profession may be assured that the serious misgivings will be allayed.—I am, etc.,

GEORGE H. MORLEY,
President,
British Association of Plastic Surgeons.

London W.C.2.

Lead Contamination of Claret

SIR,—Every claret drinker knows the incrustation on the cork and neck of an old bottle. My usual practice has been to give it a rather perfunctory wipe off before decanting. In restaurants I very much doubt whether it gets any attention at all. Sudden suspicion of its origin led me to make a few simple chemical tests which were strongly positive for lead. It is obviously derived from the lead foil used to cover the cork and is probably a mixture of acetate and carbonate. I think that this could be a source of lead poisoning in enthusiastic claret drinkers and feel that some sort of warning should be issued. My own bottles are going to have a very thorough scrubbing from now on!—I am, etc.,

G. C. MYDDELTON.

Henley-on-Thames, Oxon.

Minister on Aspirin Labelling

SIR,—You referred in your issue for November 25 (p. 1441) to a question I asked of the Minister of Health on November 15, calling for legislation to ensure that the manufacturers of drug remedies containing aspirin advertise the fact by the use of the trade name in the list of ingredients.

The Minister's reply was "No." In view of the interest shown by correspondence in your journal would you kindly publish the contents of the Minister's letter to me?

"Dear Ledger,

I am returning the papers about remedies containing aspirin which you sent to me in connection with your question.

There are two possible risks involved. One is to the relatively few people allergic to aspirin. They are, as mentioned in the correspondence in the *B.M.J.*, aware of the reaction they get from aspirin and it is surely reasonable for people liable to any allergy to read the list of ingredients on an unfamiliar package or to enquire from the pharmacist what is in it at the time they buy it. It would be impracticable to legislate to require one of many ingredients which may be associated with allergies to be designated by a prescribed description.

The other risk is irritation of the lining of the stomach, which may be what you have in mind in referring to people suffering from persistent stomach troubles; but to require manufacturers of drugs containing aspirin to describe the ingredient by that name would not deal with this risk.

Yours sincerely,

J. ENOCH POWELL."

—I am, etc.,

RON LEDGER.

House of Commons,
London S.W.1.

Diabetic Xanthomatosis in an African

SIR,—I was most interested to read Dr. J. E. P. Thomas's account (October 14, p. 999) of this syndrome. Of the 3,100 new diabetics that we have collected into the diabetic clinic of the King Edward VIII Hospital in Durban in just over three years, 579 have been Africans, and in only one have we found the classical xanthoma tuberosum of the diabetic, with the lesions on the extensor aspects of the elbows and upper forearms, and over the patellae and tibial tuberosities. In our case the xanthoma tuberosum was actually a "pre-diabetic" phenomenon, and came on fairly rapidly one year before she developed the symptoms of diabetes. The patient was a female of about 50 years of age, better nourished than Dr. Thomas's patient, without a concomitant peripheral neuritis, and with a blood cholesterol within normal limits (our laboratory work-up was not nearly as thorough as Dr. Thomas's). She responded well to insulin, and has since been converted to oral therapy.

I would make only one remark to Dr. Thomas, or other physicians writing on Africans, that diabetes is *not* a rare condition amongst them. This popular misconception dates from when African urines were not tested for sugar, though it is beginning to appear obvious that diabetes is becoming commoner in Africans. The most reliable glycosuria survey upon urban Africans is

that of Dr. H. Seftel in Johannesburg,[1] where he found an incidence of 1%—hardly putting it into the category of a rare condition. It is highly probable on the basis of our studies in Durban[2] that diabetes is very much commoner amongst those Africans living in the towns than amongst those in the country.—I am, etc.,

Diabetic Clinic,
The King Edward VIII Hospital,
Durban, South Africa. G. D. CAMPBELL.

REFERENCES

[1] Seftel, H. C., personal communication, 1961.
[2] Campbell, G. D., *S. Afr. med. J.*, 1960, **34**, 332.

Plantar Warts

SIR,—It was with interest that I read the article on the treatment of plantar warts in children by Dr. C. F. H. Vickers (September 16, p. 743). This encourages me to describe the treatment I have employed for plantar warts and found to be both quicker and less troublesome to patient and doctor.

The affected feet are immersed in a foot-bath of hot water to which one to two teaspoonfuls of soft soap are added. The soap solution has a keratolytic action, softening not only the thicker epidermis around the warts but also their fibrotic structure. After a 10 to 15 minutes' immersion, the foot is thoroughly dried and one to three drops of the following solution applied to each wart, depending on size. The solution is a mixture of one part each of salicylic and lactic acid to three parts collodion. The volatile ingredients of the collodion evaporate, leaving a film covering and adhering to the wart. The mildly corrosive and liquefying action so derived penetrates the softened fibrotic tissue deeply, gradually destroying the structure of the wart. Application before bedtime, repeated on four to six consecutive nights, is all that is necessary. The wart is then painlessly separated from the surrounding dermis, leaving a hole which slowly fills without a scar. An "elastoplast" dressing should be applied after extraction of the wart, and care should be taken to prevent the solution touching the surrounding healthy dermis, otherwise a mild inflammation may result.

A quicker method is to apply concentrated nitric acid with a glass rod; one to two drops are usually enough to destroy all of the wart. In a few patients it may be necessary to repeat the applications.—I am, etc.,

Wembley, Middlesex. JAN JAWORSKI.

"Pethilorfan" in Domiciliary Obstetrics

SIR,—The observations of Captain D. S. Smith, Major J. B. M. Milne, and Captain V. B. Whittaker (October 14, p. 1024) on the intravenous use of "pethilorfan" (pethidine and levallorphan tartrate) in orthopaedics are interesting to compare with the effects produced by the same procedure in obstetrics. Many units employ the use of local analgesia for most forceps deliveries, sometimes in conjunction with intravenous pethilorfan. I have taken this method with me into general practice and have found it to be of enormous value.

The state of hypo-aesthesia was originally induced with pethidine, but the risk of hypotension, due to respiratory depression and consequent anoxia of the medullary centres, caused this method to be fraught with danger. Respiratory depression of the foetus was another hazard but did not seem to occur. However, the addition of levallorphan tartrate to pethidine (pethilorfan) entirely eliminates these risks. A satisfactory technique would appear to be slow intravenous injection of pethilorfan, 100 mg., together with chlorpromazine, 12.5 mg., given before commencing a pudendal block. The delivery is greatly facilitated by the resultant muscle-relaxation and euphoria. The amnesic effect observed by Captain Smith and his colleagues is most marked in that the mother is co-operative throughout the delivery, falls asleep after the third stage, but remembers little or nothing of the procedure.

The small amount of chlorpromazine seems to overcome any nausea—but the usual precautions in using this drug must, of course, be observed. Promethazine has been used as an alternative to chlorpromazine, but it has recently been suggested that this drug has an anti-analgesic effect.—I am, etc.,

Maidenhead, Berkshire. MICHAEL IRVING.

Lignocaine with Adrenaline

SIR,—In 1955 Dr. W. A. W. Dutton and I described a technique of local analgesia for forceps delivery. Following our article there were reports of severe toxic reactions where 1% and 2% lignocaine had been used instead of the 0.5% solution which we recommended.

Dr. R. A. Deacock (October 14, p. 1025) has again drawn attention to this danger. It is easy to inject more than 50 ml. of solution into the perineum, and I believe it is proper to do so for forceps delivery. The 0.5% solution is completely effective and higher concentrations may be dangerous.

The toxicity of lignocaine is more geometrically than directly proportional to its concentration. Thus 50 ml. of 1% solution is more toxic than 100 ml. of 0.5% solution. It would be a pity if the excellent safety record of local analgesia in obstetrics were marred by simple errors of dosage.—I am, etc.,

Banbury. J. M. GATE.

REFERENCE

[1] Gate, J. M., and Dutton, W. A. W., *Brit. med. J.*, 1955, **2**, 99.

Elastic Ankle-bands and Cramp

SIR,—I think I can explain Dr. R. W. Smithells's problem of nocturnal calf-pain (November 11, p. 1293), having myself suffered from this condition. I have found I can induce intense pain in either calf by forcibly plantar-flexing the appropriate foot. This sends the calf muscles into spasm, hence the tense feeling in the muscles. Instant relief is obtained by firm and resolute dorsiflexion of the foot, automatically relaxing the muscles in spasm. This I feel is the logical explanation of many nocturnal cramps. It is very easy to plantar-flex excessively when lying in the prone position as many do when in bed.—I am, etc.,

St. Helens, Lancs. C. D. ELLIS.

The Tiger's Nose

SIR,—Although I have never hunted tigers, I have lived with many domestic cats and have always been interested in the dryness of the cat's nose when compared with the wet-nosed dog.

The late Professor Wood Jones[1] endorsed the comment of Dr. W. T. Simpson (October 28, p. 1152) and the big-game hunters when he stated that, "The wet-nosed dog hunts by scent, the dry-nosed cat by sight. The wet-nosed dog follows its victim's trail, the dry-nosed cat stalks it." Earlier on he remarks, "It

may not be obvious to dry-nosed man what advantage there may be in having a rhinarium of which the naked skin is constantly moist. Yet the advantage is real enough. When the wind is light, so light that one can see nothing moving that will tell the direction whence it blows, old sailing-ship sailors will moisten a finger by licking it and, holding it aloft, feel on its moistened surface the presence of what little wind there is. The moistened surface soon detects the presence of the moving air and appreciates from which direction it is moving. A wet-nosed animal we would therefore expect to be an animal endowed with a high degree of olfactory sense and, moreover, one to which it was important that the direction whence the scent came should be realized. The wet-nosed animal might be the hunter or the hunted; to be efficient in either case a knowledge of whence comes the scent is essential.

Wood Jones's whole exposition of the rise and fall of the "smell brain" is a fascinating story. He goes on to show that scent becomes replaced as the dominant faculty once an animal leaves the earth, whether it takes to the water, the air, or the tree-tops. As members of the feline family are nearly all excellent climbers this would fit in with their dry-nosed state.

Although the larger carnivora of the cat tribe may have little or no sense of smell it would be very difficult to accept this as being true of the domestic cat. Nevertheless it is a matter of common observation that the cat does hunt and stalk its prey by sight rather than by smell.—I am, etc.,

Liverpool 12. S. E. KEIDAN.

REFERENCE

[1] Jones, F. Wood, and Porteus, S. D., *The Matrix of the Mind*. 1929. Edward Arnold, London.

Consummation of William Harvey

SIR,—On reading "The Consummation of William Harvey" by Sir Arthur Thomson (November 18, p. 1303) I disagreed with the statement in the conclusion that we should not attribute too much importance to empirical experience. This is inconsistent with the next statement that unquestioning belief in accepted doctrine is dangerous. Would not Sir Arthur's Calvinistic governess be more pleased if it were said that the moral was that we should observe first and explain afterwards? Empirical means that which is based on experience and not theory. There is, I agree, a colloquial use of the term empirical which has no strict definition, but implies that the relevant experience is insufficient. It would be better to discard the word used in this sense, as it can confuse the unwary.

Apart from the conclusion, Sir Arthur's dissertation was so abundantly clear that I feel the Calvinistic governess would be better employed influencing some modern intellectuals who are loath to draw any moral or conclusion, and who behave as if they believed muddle-headedness to be the key to all knowledge.—I am, etc.,

Hartfield, Sussex. PETER DUPRÉ.

Alcoholism and Partial Gastrectomy

SIR,—I have been struck by the fact that of the last thirteen alcoholics referred to me through various channels seven had partial gastrectomies during the course of their alcoholism which did not appear to alter the course of the condition but cured the gastric symptoms. The sufferers varied from one of the landed gentry to an unemployed sailor and included one middle-aged woman, a doctor, and a scientist, and the latest is an R.A.F. officer recently demobilized. Their ages varied from 63 to 32.—I am, etc.,

Blackpool. B. G. KELLY.

Clinical Study

SIR,—Professor J. McMichael's Croonian Lectures on hypertension (November 11, p. 1239, and November 18, p. 1310) provide a valuable review of this complex problem, but I was mildly surprised to read his statement—"Detailed clinical study must dominate and guide our laboratory and experimental approaches." Such studies are obviously important, but they did not give us penicillin, the supreme but by no means the only instance of the conquest of disease entirely by laboratory workers.

The notion that clinical studies bring an extra-special whiteness and brightness to the fabric of medicine is alluring—at any rate to the clinician—but the laboratory worker may be pardoned for preferring Brand X.—I am, etc.,

London S.E.5. F. B. BYROM.

Unwanted Free Beer

SIR,—If Dr. A. Spencer Paterson (November 11, p. 1293) and Dr. James Simpson (November 25, p. 1436) will send me their unwanted free samples of alcoholic beverages I will see that they are suitably disposed of. Happy Christmas!—I am, etc.,

Sheerness, Kent. MICHAEL F. HAWKINS.

Registration of Congenital Deformities

SIR,—There is to-day a growing knowledge of factors concerned in the formation of congenital deformities. Some of them are associated with demonstrable faults in the chromosomes. In others the factors may operate on the developing foetus. Some of these are known—such as irradiation by *x* rays or by radioactive fall-out, others by drugs or toxic conditions. There appears to be an increase in incidence; certainly more patients are being referred for surgical treatment. There is, therefore, a need for accurate comparative figures to show any trend in incidence.

Registration by statute of all obvious congenital deformities at birth would, in my opinion, be more valuable and realistic than, for example, the registration of measles. I feel sure that all concerned with these deformities, whether in research or management, would welcome such a step.—I am, etc.,

Department of Plastic and Jaw Surgery,
Frenchay Hospital,
Bristol. D. C. BODENHAM.

POINTS FROM LETTERS

Shrunken Numbers

Mr. H. LIVINGSTONE PEAKE, F.R.C.S. (Eldoret, Kenya), writes: I was delighted to read the letter by Dr. John Mills anent the above (September 30, p. 895), because I have many times been on the verge of writing to you during the past ten years to ask if you could not use your influence to prevail upon certain drug houses to use larger print on their vials and ampoules or the accompanying slips of paper. . . . Pity the poor doctor who has to attempt to read such stuff in some indifferently lighted house or cottage.

Obituary

H. HILTON STEWART, M.D., F.R.C.P.

Dr. H. Hilton Stewart, neurologist to the Royal Victoria and City Hospitals, Belfast, died in that city on November 25. He was 60.

Howard Hilton Stewart was born on December 3, 1900, a son of the late Andrew W. Stewart, editor of the *Belfast Telegraph*. His early education was at the Royal Belfast Academical Institution, and he graduated M.B., B.Ch. of the Queen's University of Belfast in 1923. After holding resident appointments in the Royal Victoria Hospital and the Ulster Hospital for Children and Women he became a house-physician and afterwards registrar in the Hospital for Paralysis and Epilepsy, Maida Vale. On his return to Belfast he was elected to the staff of the Ulster Hospital in 1938 and later became medical consultant to the Ards District Hospital.

Always interested in neurology, he became an honorary physician to the Claremont Street Hospital for Nervous Diseases. There it may be truly said that he effected a transformation. Handicapped as it still is by unsuitable premises it has become an excellent example of what a small special hospital can be, and Hilton Stewart will always be regarded as its second founder. Subsequently he became neurologist to the Royal Victoria Hospital and the Belfast City Hospital. He obtained the Membership of the Royal College of Physicians in 1928, being elected a Fellow in 1951. He was a past-president of the Ulster Psycho-Neurological Society.

R. M. writes: Hilton Stewart was a man of high ideals—and lived up to them. An elder of Elmwood Presbyterian Church, his religion was in his heart rather than on his tongue. His very simplicity of nature was reflected in his work. He was guided by first principles and was incapable of guile. He could state his opinion so clearly and so modestly that his reports on clinical problems were very highly valued by all who sought him. His chief recreation was golf. He loved his foursomes at Newcastle on Saturday afternoons, and what a delightful companion he was on any occasion. His wife (née Clara dos Santos) died some six years ago, and Hilton never really recovered from his bereavement. In January last he was discovered to have a fatal malady: his courage and cheerfulness in the months which were the residue of his life have been and will remain a source of wonder and of inspiration to all his friends. He was indeed a very gallant gentleman.

Dr. R. S. ALLISON writes: Many men possessing deep reserves of natural courage are never called upon during their lifetime to display these. Hilton Stewart was an unassuming person who did not care for publicity, and few of us may have guessed that he possessed to such a high extent that quality of courage in adversity which he showed throughout the long year of his final illness. Although he recognized its nature at an early stage he did not become weighed down by it but instead carried on with his hospital work and private practice as usual. One of his last public appearances was to preside at the Cecil Calvert memorial lecture in the Medical School, and the simple grace and dignity which he gave to this occasion drew murmurs of admiration from all those who were present.

As a clinical neurologist he was most able, and, although always keeping abreast of modern advances in contrast radiology and electroencephalography, he remained faithful to his early clinical training in London at Maida Vale under Douglas McAlpine and Russell Brain, setting clinical examination of the nervous system before all other methods of approach. A special interest of his was the follow-up and control of patients suffering from epilepsy, and, although essentially a neurologist in his outlook, he did not avoid psychoneurotics, in the diagnosis and treatment of whose conditions he was convinced the neurologist had an important part to play. But it was in his work as an administrator when he became chairman of Claremont Street and Killowen Hospitals in 1948 that probably his greatest achievements lay, and it is no exaggeration to say that it has been largely through his own devotion and that of his wife, the late Clara Hilton Stewart, who died six years ago, that Claremont Street Hospital occupies the respected position it does to-day.

G. McF. writes: The death of Dr. Hilton Stewart has left a great gap in the lives of the people of Northern Ireland, and especially among his associates in Belfast. He was a very live personality. His quick wit, critical mind, and wide knowledge could not but make a vivid impression in any community. Dr. Stewart was a very gifted general physician as well as being a bright light in his own specialty of neurology. Probably his greatest contribution to his own and future generations was his work for those unfortunates suffering from nervous disorders. The rise of Claremont Street Hospital for Nervous Diseases from being a small semi-private dispensary to its present proud status as a world-known and much-respected modern hospital for nervous diseases owes more to Dr. Stewart than to any other man. The development of this hospital showed his own clinical ability, his political acumen, and his breadth of mind, in that he was able to attract the confidence of the general medical practitioner and his patients, the support of the financing authorities, and the co-operation of his gifted neurological colleagues. One could say that the present hospital is his memorial.

For me there has been a great personal loss. We had been intimate friends since I became attached to the Ulster Hospital in 1925 and he was my house-surgeon. Every child under his care then was known by its Christian name. We shared adventures in those days when one travelled with one's anaesthetist to operate in an outlying farm or village. Dr. Stewart was then my skilled anaesthetist, as shown by his ability to produce deep anaesthesia with open ether on an open mask. The skill of those days he turned eventually to his deep and final interest in neurology. I am thankful that I was permitted to know him for so long. As a surgeon I learned much from my association with such a critical and learned physician, and it is difficult to measure the great debt I owed him in professional knowledge, not to speak of his comradeship with his active mind and witty sallies. Above all I owe much to his professional skill, endowed with loving care, which he brought to the bedside of any sick person in the family. His passing away has created for us a great void.

His friends and colleagues will miss him greatly. They will miss his ready wit, his ability as a raconteur, when he snatched the humour out of a trivial experience and restated it with his own unmatched dialectical exuberance. They will miss his company on the golf course. His car driving was an outward sample of his quick cerebration—quick, skilful, and perfectly safe. He enjoyed meeting his friends in the Royal County Down Golf Clubhouse, but when he was on the golf course he was down to very serious business. He enjoyed "the rigour of the game."

Such things were the outward man. Inwardly he was a man with strong religious principles. He felt honoured when he was elected an elder of his Presbyterian Church and took his duties seriously. He was a firm believer in total abstinence and was himself a strict teetotaller. He had been a non-smoker for the last thirty years. In his dealings with humanity he tried to follow his Master's footsteps and did not count the cost. Many of his patients were beholden to his Christian charity. His deep spiritual feelings exuded through his professional advice to the psychically disturbed. His patients grew to love him and depend upon him.

The last months of his life were an example to all. Although he knew he was suffering from an incurable disease and had not many months to live he never complained, but

tried to carry out his life's work right to the end. We are grateful that in his last days he had not a prolonged time of suffering and that he passed quietly away, his life's work well done.

I. F. writes: The death of Hilton Stewart brings to an end an unbroken personal friendship of 50 years. It is easy to look back now to the schoolboy whose integrity and thoughtfulness for others were his cardinal features, and to realize that they were to make friends for him throughout life. They carried him through his undergraduate career and helped him through the struggle of early consultant practice and finally ensured for him the love of his patients and the esteem of his friends and colleagues when he had reached the peak of his profession in the field of neurology. The crowded memorial service testified to the deep feeling that all—both medical and lay friends—felt for this modest, friendly, if at times lonely, man. In his active life he was a model to many of us—young and old. When faced with a mortal illness—a disease for which he himself had helped so many over the last 35 years—his courage in the last 12 months was the admiration of us all. Rarely is a man privileged to give so much in his living and even more in his dying.

ROBERT STANDISH-WHITE, C.B.E., F.R.C.S.I.

Mr. Robert Standish-White, emeritus surgeon to the Bulawayo General Hospital and a former president of the Medical Council of Southern Rhodesia, died on October 14 after a short terminal illness. He was 73.

Robert Standish-White was born in Dublin on May 1, 1888, and received his early education at the Presbyterian College there. He qualified from the Royal College of Surgeons of Ireland in 1909, and became L.M. from the Rotunda in the same year. He proceeded F.R.C.S.I. in 1914. From an appointment as a resident surgical officer in Dublin he was persuaded by the late Dr. W. May, then Director of Medical Services, Northern Rhodesia, to accept an appointment as surgeon to the Livingstone Hospital in 1911. This post entailed journeys to many smaller centres and provided a wide variety of cases. Soon afterwards he transferred to the sleeping-sickness unit established by the Chartered Company, and worked with Worrington, Yorke, Kingsley, and Leech in the Namwalia, Fundu, and Luangwa Valley areas.

On the outbreak of war in 1914 he resigned his appointments to volunteer for service with the R.A.M.C., and was seconded to the Northern Rhodesian Rifles. Commissioned major, he served with the famous "Murray's Column," which suffered very heavily from wounds and disease. For his work in this campaign, and later in France, he was appointed O.B.E. in 1919. Demobilized, he spent a year in postgraduate study in London, and then began practice in Bulawayo, Southern Rhodesia, where for 35 years he was the leading figure in surgery. His colleague and contemporary, Lord Malvern, may have made a bigger impact on the outside world. But even now it would be hard to find a town in the Rhodesias which does not hold a patient upon whom Standish-White had operated.

He was president of the Matabeleland and Northern Rhodesia Branch of the B.M.A. in 1929–30, a member of the Medical Council of Southern Rhodesia for some twenty years, and president of this Council from 1943 to 1951. A duodenal ulcer which perforated just prior to embarkation at Capetown in 1940 prevented him from undertaking active service during the second world war, but his tremendous exertions as consulting surgeon to the Rhodesian Air Training Group of the R.A.F. during this conflict brought him well-merited recognition in his promotion to C.B.E. in 1945.

After retirement from active practice in 1953 he devoted his undiminished energies to many paramedical pursuits. As director of Red Cross personnel, an energetic member of the committee of the Bulawayo Blood Transfusion Service, and as honorary medical director of the King George VI Memorial Children's Centre for the Physically Handicapped, he gave unstintingly of his time, wisdom, and engaging personality. In recognition of his services as honorary consulting surgeon to the Bulawayo General Hospital for more than twenty years, the Minister of Health conferred on him the title of Emeritus Surgeon to the Bulawayo General Hospital in 1954, the first occasion on which such an honour had been bestowed in Rhodesia.

In 1923 he married Winifred Kellman, daughter of Sir William Chandler, K.C.M.G., and she survives him. Of his three sons, one is following his father's footsteps in surgery.

W. H. writes: No cold obituary of Robert Standish-White can give the reader a true impression of the warmth and kindliness of his personality. He loved his patients, his work, and his friends, and his physical presence radiated this message. His charm of manner was indescribable and, like his skill, was available to all. He was probably seen at his best when dealing with an abdominal emergency in the small hours of the morning. His Irish wit and irrepressible enthusiasm for work kept all about him on the alert from the deft pre-operative examination, through the scrupulously correct operation, to the final careful instructions about post-operative treatment.

His passing leaves a sad gap in our ranks. A general surgeon in the best sense of the term, he set the example for the high standards of medical practice which obtain in the land of his adoption. An inspiring leader, an exemplary teacher, a charming companion, and a loyal friend, he will be mourned by many in all walks of life.

G. M. MAYBERRY, L.R.C.P.&S.I., L.A.H.

Dr. G. M. Mayberry, formerly medical superintendent of Dagenham Sanatorium and Langdon Hills Sanatorium for Children, died at his home in Frant, Sussex, on November 21. He was 78.

George Mahony Mayberry was born on July 24, 1883, the only son of Dr. F. G. Mayberry of Kenmare, Co. Kerry. Educated at St. Columba's College and Trinity College, Dublin, he qualified in 1911. In his student days he was a fine athlete and represented the United Kingdom at the Olympic Games in 1908. Apart from four years in the R.A.M.C. in the first world war he spent all his medical life as a tuberculosis physician. A sound clinician of the old school, for thirty-five years he was medical superintendent of Dagenham Sanatorium and Langdon Hills.

Born and bred in Kerry, where his forbears had been doctors for two generations, he was a great lover of the country and a keen fisherman.

To his widow and three daughters who survive him we extend our sympathy.

Dr. E. ASHWORTH UNDERWOOD writes: The death of my old friend and colleague George Mayberry brings back memories of the many years which he devoted to the care of tuberculous patients from an industrial region of Essex. As medical officer of health of the county borough of West Ham from 1937 to 1945 I must be one of the few men now surviving who can speak from extensive first-hand knowledge of his work. It is interesting to reflect that his active life covered virtually the whole of the period of the official treatment of tuberculosis as such in this country. The position was that in 1911 the Local Government Board issued regulations which made pulmonary tuberculosis compulsorily notifiable. In this same year the National Health Insurance Act was passed, and it was to come into operation in July, 1912. The West Ham county borough council had from 1911 been considering their future action with regard to the institutional treatment of tuberculosis, and they contemplated purchasing a site for a sanatorium at Langdon Hills. But this site was a long way from West Ham—how far may be judged from the fact that on a clear day Southend pier can easily be seen from it—and it was considered that some accommodation closer at hand should be made available, at least as a temporary measure. To this end the council, on the advice of Dr. Charles Sanders,

the medical officer of health, decided to utilize their smallpox hospital at Dagenham, which had been built in 1899. This course was approved by the Local Government Board, which recommended that a resident medical officer should be appointed to the temporary sanatorium. George Mayberry, a graduate in Arts of Trinity College, Dublin, and a product of the Dublin school of medicine, who was then at Benenden Sanatorium, was appointed and commenced his duties in April, 1914.

During the nine months which elapsed until the end of 1914 Mayberry admitted 190 cases. But the country was by then in the throes of war, and he, of course, joined the R.A.M.C., in which he served as a captain until 1919. On his return he became engrossed in his tuberculosis work, but there was soon to be another interruption. From April, 1920, until near the end of July, 1922, Dagenham Sanatorium was closed to tuberculous patients because the hospital had to be reserved for smallpox patients. The council thereafter made other arrangements for smallpox, and from 1922 until his retirement in 1949 Mayberry was able to devote himself entirely to the running of Dagenham Sanatorium—as it was now named—and of the sanatorium for children which had been built on the Langdon Hills site.

Mayberry was a sound clinician and he had the welfare of his patients ever in the forefront of his mind. There must be many former patients who remember with gratitude the skill and attention which he devoted to their treatment. When in later years he was able to take advantage of radiological facilities and the operation of artificial pneumothorax, then widely practised in pulmonary tuberculosis, he threw himself into his work with enthusiasm but with caution. His passing removes one of the shrinking band of men who fought valiantly against tuberculosis in the pre-antibiotic days when it was truly a scourge.

RUTH DARBY, M.B.E., M.B., Ch.B.

Dr. Ruth Darby, who had practised in Maidstone for 30 years, died suddenly on October 19 after a short illness. She was 74.

Ruth Darby, who was a member of a well-known Quaker family, was born in Birkenhead, and educated at the Mount School, York, and at Birmingham University, where she excelled at games, particularly hockey, being captain of Warwickshire. In 1922 she graduated M.B., Ch.B. and held house posts at her teaching hospital. She went then to the Infants' Hospital, London, as pathologist, and with Dr. Donald Paterson, of Great Ormond Street, she wrote a paper on infant feeding.

Ruth Darby practised first in Wembley Park. In 1928 she married Roy Cavander Lancaster, now Clerk of Assize to the South-east Circuit, and three years later accompanied him to Maidstone, where for several years she was the only woman medical practitioner. She built up a large practice, with paediatrics and midwifery as her special interest. During the second world war she was in charge of a military families' hospital and she was awarded the M.B.E. for her services. Another great interest was the work of Dr. Barnardo's Homes: until her death Dr. Darby was medical officer to the Home at Yalding, near Maidstone.

Ruth Darby was a careful and conscientious doctor, but her patients thought of her first and foremost as a friend and sought her advice on problems quite unconnected with illness, but none the less, she would have said, the real concern of the good family doctor. In her latter years osteoarthritis frustrated and restricted her, but she would struggle undaunted up difficult stairs despite increasing pain and disability, and to her patients her warm and courageous personality expressed the ideal "To comfort always" in its fullest sense. She spent herself in the service of her patients, and the large number attending the Memorial Service to her bore witness to the great affection and respect in which she was held. To her husband the sympathy of hundreds of grateful people must have brought some comfort in a great loss.—J. E. R.

CHARLES REID, M.D., D.Sc., D.P.H.

Dr. Charles Reid, formerly professor of physiology in the medical faculty of Abbassia, Ibrahim Pasha University, Cairo, and until recently W.H.O. professor of physiology at Dow Medical College, Karachi, died on October 24. He was 69 years of age.

Charles Reid, who was born at Cove, Kincardineshire, on May 9, 1892, was educated at Robert Gordon's College and at the University of Aberdeen, where he had a distinguished career, graduating M.A., with honours in mathematics and natural philosophy; B.Sc., with special distinction in physiology; and, in 1917, M.B., Ch.B., with honours. He proceeded M.D., again with honours, in 1926 and D.Sc. in 1927. After holding the posts of house-surgeon and house-physician at the Royal Infirmary, Aberdeen, he was on war service with the R.A.M.C. from 1917 to 1920. Returning to his own university, he held in turn the appointments of assistant in physiology and lecturer in experimental physiology. He was also at one time acting head of the department. During this period he wrote many papers on the vascular system and in particular on blood pressure. From 1929 to 1932 he was professor of physiology at the Prince of Wales Medical College, Patna, India, and examiner in physiology at several Indian universities, and then, after holding a Commonwealth research fellowship for a year, he became lecturer in physiology at University College, London. In 1937 he was appointed reader in physiology at the London Hospital Medical College. After the war he went abroad again to become professor of physiology in Cairo, and shortly before he retired to live in Haslemere, Surrey, he held a W.H.O. professorship at the Dow Medical College, Karachi.

Charles Reid was a courteous, mild, and retiring man, but meticulous and pertinacious in both teaching and research. He got on well with his colleagues and students. He seemed to have a liking for the Far and Middle East, and perhaps because he had a certain wanderlust he did not settle in any appointment for more than a few years. But wherever he went he helped his students to acquire a thorough knowledge of physiology.

Dr. Reid married Edith, younger daughter of Robert Laing, of Aberdeen, and they had one daughter.

S. G. VINTER, M.R.C.S., L.R.C.P., D.P.H.

Dr. S. G. Vinter, who formerly practised in Torpoint, Cornwall, died at Walton-on-Thames on November 9. He was 97 years of age.

Sydney Garratt Vinter was born in London on December 27, 1863, the son of the artist John Vinter, R.A. From St. Paul's School he went on to St. Mary's Hospital to study medicine and qualified in 1887. After a short period as a ship surgeon and a few months as a Government medical officer in Perak he settled at Torpoint and remained there until his retirement in 1925. He held several appointments in the area, was a justice of the peace for the county of Cornwall, and became medical officer of health of the Torpoint Urban District when it was first formed. He had taken the D.P.H. in 1953. During the first world war he served as a captain in the R.A.M.C., at first on general duties and then as sanitary specialist for the Dorset Training Area, being mentioned in dispatches for his work in this appointment.

On his retirement Dr. Vinter went to live at Shepperton-on-Thames, where he became interested in the Boy Scout movement, in which he continued to take an active part until he was 90. Only a few months ago he was present at the dedication of a stained glass window in St. Nicholas Church, Shepperton, to commemorate his 30 years as a group Scoutmaster in the district. He married Frances Toms in 1893. She died in 1926, and he is survived by a son and two daughters, the former and one of the latter being in the medical profession. His elder son was killed in action in 1916.

H. L. APTHORP, M.D.

Dr. H. L. Apthorp, who practised in Harrow for many years, died on November 18, aged 87.

Hugh Llewellyn Apthorp, who was born on June 21, 1874, graduated M.B., C.M. at the University of Edinburgh in 1897. After holding the posts of house-surgeon at the Devonshire Hospital, Buxton, and resident medical officer at the Royal Albert Hospital and Eye Infirmary, Devonport, he served as a civil surgeon in the South African Field Force. On his return to Britain he settled down to general practice in Harrow, where he remained for the rest of his life except for a period of service in the R.A.M.C. during the first world war. He was in partnership for a time with the late Dr. Wansbrough Jones, but later they practised separately. In 1931–2 Dr. Apthorp was chairman of the Harrow Division of the B.M.A.

H. E. T. writes: I first met Dr. Apthorp when he had been in Harrow for about seventeen years. I was his nearest neighbour in practice and found him very friendly and helpful to a young man alone in practice. He did a lot of work at Harrow Hospital in the days when this was a cottage hospital and there were no house officers. If anaesthetics were required Dr. Apthorp was willing to help and co-operate generally. In the 1920's he did a good deal of minor surgery at the hospital before we had a large consulting staff as at present. He was a genial friendly companion with a very keen dry sense of humour. As a practitioner his attitude to his patients was fatherly. He married in middle life and his widow survives him. He also leaves a son, who is a medical registrar at St. Bartholomew's Hospital.

W. P. RICHARDS, M.B., Ch.B.

Dr. W. P. Richards, who practised in Bedford for a number of years, died on September 27 aged 59 years.

William Powell Richards was born in Brisbane, Australia, and there spent his schooldays. His father and mother were both natives of Herefordshire and emigrated to Queensland shortly after their marriage. Determined to be a doctor, William came over to Britain and studied medicine at Aberdeen University, where he graduated M.B., Ch.B. in 1925. After a series of "locums" and an assistantship he settled in the village of Kempston, some two miles from Bedford, and continued to practise there—latterly with two partners—until his death from ischaemic heart disease.

Devoted to the interests of his patients, to whom he became, over the years, "guide, philosopher, and friend," he was greatly beloved. His outside interests were few. Brought up in a musical atmosphere, he was in his earlier years a good pianist, but through stress of work he was later forced to neglect an accomplishment which was a great joy not only to him but to others. His abiding passion, however, was not music but the study of foreign affairs. Towards the end of his life he came to know only too well that his days on earth were likely to be few, but in spite of this knowledge and recurrent attacks of agonizing pain he gallantly "kept right on to the end of the road." Late in life he married an old friend of his, and to her we extend our sincere sympathy.

A. C. WHITE KNOX, C.B.E., *M.C.*, M.B., Ch.B.

The obituary of Dr. A. C. White Knox was published in the *Journal* of November 25 (p. 1438).

Dr. N. W. HAMMER writes: As one who had known the late Dr. A. C. White Knox since 1924, may I add my words of appreciation? With experience as a general practitioner, as a temporary captain in the first world war, and as a Home Guard medical officer in the second, with no higher qualifications and no history of administrative service or of senior employment, he was selected, no doubt from among many, to be Surgeon-in-Chief of the St. John Ambulance Brigade and Principal Medical Officer of the St. John Ambulance Association—a great tribute to his charm, his personality, and his felicity in contacts. I remember how, early in the last war, he mentioned to me his great desire to rejoin the R.A.M.C., and his disappointment when he did not obtain his wish, since commissioning only in the rank of lieutenant was at that time available. The first-aid publications, with the preparation of which he was, with others, concerned, are all marked by very great care taken to make their teaching thoroughly sound. He did not even obtrude any personal opinions or personal didacticism or dogmatism, and used his influence to ensure that what was included followed, even sometimes as far as almost verbatim quotation, the lines of official and non-official books whose teachings had been proved by experience. He was indeed a big man, in stature and in powers of personality. There are not many like him. He was much respected.

Medical Notes in Parliament

GROWING SHORTAGE OF DOCTORS: CAUSES, CONSEQUENCES, AND REMEDIES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Willink 10% cut in the intake of preclinical medical students (recommended in 1957) has been reviewed and is to be reversed. "The Government are satisfied that the prospective demand for medical services would justify a rise in the university intake from Great Britain of 10% above the level recommended by the Willink Committee. This was a figure of 1,760." Thus Lord NEWTON, speaking for the Ministry of Health, answered the debate which Lord TAYLOR initiated on November 29 about the growing shortage of doctors, its causes, consequences, and possible remedies.

The University Grants Committee, Lord NEWTON said, had been asked to consider with the universities the implications of the Government's conclusion, and it would be premature to say more about the numbers and capacity of medical schools—except that it was hard to imagine that the Government would approve of the very large increase which Lord Taylor had called for in his opening speech.

Lord Taylor's Case

Much of the argument was conducted in terms of figures and calculations from Willink onwards, which were admitted to be imprecise and uncertain. For example, Lord Taylor's case, in its simplest and shortest form, was—an increase of the general population between 1939 and 1958 of 10%; increase in medical students, 7%; between 1948 and 1960 55% increase in the number of consultants. Professors François Lafitte and J. R. Squire had concluded last year that as a matter of urgency the number of medical students ought to be stepped up, otherwise a crisis might emerge around 1965, and be much harder to deal with. "Even they were optimistic, for the crisis is here now," commented Lord Taylor.

Here the Government and the critics were much nearer to agreement. Lord Taylor put third among his remedies a proper statistical department at the Ministry of Health to review continuously and intelligently—a proposal later endorsed by Lord EVANS—the state of the Health Service. If there had been such a department seven years ago, he said, "this mess' would never have occurred. On this aspect Lord NEWTON said that action was being taken to improve the statistical information. Nevertheless uncertainties would remain. The solution did not lie in attempting to make firm estimates at wide intervals in time, but in constantly watching the figures, including those of output from the medical schools. This the Government intended to do.

Four Remedies

Lord TAYLOR, reviewing the medical services, concluded, "We cannot solve our hospital problem and we cannot solve our general practice problem without more doctors," and advanced four remedies. The repudiation of the Willink Report and the improvement of the statistical background have already been mentioned. The third was that one must have at least three, and preferably six, new medical schools at once. "I suggest, as a crash programme, that we open first-year medical courses next October at, say, Southampton, the Central Middlesex Hospital in North London, and Nottingham." This would give time to build up the teaching for the second and subsequent years. All that was needed was hutted laboratories and the first-year teachers. Given the proper sense of urgency both could be produced in time. In Birmingham and Manchester there was room for second medical schools taking the local university degrees. There were regional board hospitals with first-rate consultant staffs in both cities who could soon rival those already established.

Finally, again as a crash operation, we must do something to fit our medical colleagues coming from the less-developed countries for the work they have to do here. We should at once establish four short-course, intensive training centres to which immigrant doctors could go for six to eight weeks, to be taught about the work they were going to do, about the Service, the patients, and their own role especially in relation to other doctors, as well as ordinary emergency casualty medicine and surgery; and to be placed properly, according to their capacity and our needs.

Immigrant Doctors

The first of these passed without comment from the Government spokesman. On the second Lord NEWTON deplored exaggerated criticisms of the language difficulty while admitting that there were dangers in excessive reliance on doctors from abroad, and expressed the Government's hope that these doctors would continue to make a valuable contribution to the hospital service. The idea of special training found no favour with him. It ignored the fact that appointing authorities had complete discretion. To insert such a "training school" between one group of registered practitioners and their potential employers would be a slur both on the qualifications and training of overseas applicants and the prospective employers, who were expected to exercise an informed discretion in their appointments.

Lord EVANS thought it to be true that without the 3,600 doctors from overseas—one-quarter of all house officers—the Health Service would not grind slowly to a standstill, but break down completely. At the same time it was impossible to gain entry to a medical school until possibly 1963, and "only possibly" then. Most teaching hospitals in his opinion could easily and without disadvantage take an extra 10% of students. The real difficulty was the bottleneck in preclinical subjects—getting the number of teachers required and the necessary accommodation.

In Defence of Willink

Lord COHEN OF BIRKENHEAD, a member of the Willink Committee, was concerned first to correct the easy assumption that all the Willink Committee had done was to recommend a 10% cut in student intake. The Committee came into being because of grave concern that there was a surplus of doctors. Yet after a searching examination of the evidence it recommended an immediate increase of 625 in the number of general practitioners, plus 75 a year more; a yearly increase of 160 in the number of consultants and specialists until 1965, and about 80 thereafter, with similar increases in junior staff; and 175 more in preventive and social medicine. After developing the defence further, pointing to the speculative nature of the Committee's assumptions and calculations, acknowledged at the time, and the discovery in 1959 that some of these assumptions were being falsified by events, he conceded that on the 10% reduction the Committee were wrong. But there had not been this 10% reduction. There was no accurate source where the number of students admitted to the medical schools could be found, but the Report on Medical Staffing showed that in 1958 there were 1,675 graduates from British medical schools, and in 1962 (the first year when the cut could have any effect) there would be 1,691, rising to 1,730 in 1964. So the Willink recommendation could not possibly have had the influence attributed to it.

The crux of the matter, Lord Cohen continued, was not whether the Willink Committee had been right or wrong, but "Are there sufficient doctors?" He examined in some detail the question of Commonwealth practitioners (rejecting Lord Taylor's suggestion of training and selection centres as illegal under the 1956 Medical Act in many cases and impracticable in others, but accepting the need for help with the language difficulty), the general practitioner, maximum list, and the deployment and training of hospital staffs, and reached the conclusion that there was a need for more doctors, and that the first step should be forthwith to increase the intake by approximately the figure Lord Taylor had put forward—250 students each year, or about 10% above the Willink figures.

Lord Cohen's Prescription

Lord Cohen's ideas for achieving this were: (1) To invite the medical schools which had made a cut to restore it, so that they had their Willink numbers (of 1956). (2) To increase the intake if possible into the preclinical years. There might be a possibility of enlarging these facilities in existing universities. If it were done, it might well give the 250 rise immediately. It might become necessary to establish new medical schools, one or more, although not in association with a hospital; all medical schools should be integral parts of universities, and he would prefer to see a new medical school associated with a northern university.

He emphasized, in conclusion, that the supply of doctors was a dynamic problem, subject to changes in scientific and therapeutic knowledge, and therefore demanding, as others had said, a regular annual review of graduates, student intakes, and the like, so that immediate decisions could be taken.

General Practice

Distribution in general practice as well as staffing in the hospital service came under investigation during the debate, and some Ministerial comments may be noted briefly. In Great Britain the number of doctors employed in 1956 was 18,537 (whole-time equivalents), and in 1960 it was 20,148. In general practice the numbers were respectively 22,551 and 23,291. There are also about 2,500 doctors employed wholly or mainly by local authorities. In only one year of the five was the percentage increase of population greater than the percentage increase in general practitioners, and then only slightly because of the exceptional circumstance of superannuation. So far 623 junior posts in hospitals in unattractive areas have been approved for the special allowance of £100. The staffing review recommended by the Platt Committee will cover not only immediate circumstances but also the needs of the next few years. In 1952 more than half the population lived in areas designated as needing more doctors; in 1960 those areas contained only one-fifth of the population. The Ministry of Health, the Medical Practices Committee, and the General Medical Services Committee are shortly to discuss whether any further measures could be taken to alleviate the difficulties.

LEAD IN FOOD AND DRINK

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Dr. BARNETT STROSS (Stoke-on-Trent, Central, Lab.) views the Lead in Food Regulations (S.I. 1961, No. 1931) with great disfavour, and on November 30 moved a technical motion to have them annulled in order to express his disapproval. They are based on the revised recommendations

of the Food Standards Committee, and, quite apart from the fact that it is seven years since the recommendations were made, Dr. Stross thinks they are not good enough.

He gave the House several examples of why he thought so. Admitting that it was impossible to expect food to be entirely free from lead, since it was found in minute quantities virtually everywhere and in almost everything, he claimed that it should not be added to by gross mistakes in the manufacture and handling of food and that the use of lead or lead alloys in food should be avoided.

Port and Claret

With a passing reference to the possibility that oysters could be found with 80 parts in a million in them from very polluted water, he asked why no limit was placed on the amount of lead in drinking-water; there were other metals that could be used for conducting it, and this was the plastic age. Beer could be heavily contaminated if lead pipes were used; and cider and perry were even more dangerous because they could be contaminated by lead sprays on the fruit and by other means in manufacture. Why should wines at one part per million still be allowed, but vintage port be left out of the regulations? This had all been discussed with the wine trade since 1954, but there was no suggestion in the regulations about when, if ever, wine was to become safe to drink.

When wine was fermented the lead tended to come out, but then came the unhappy business of the lead cap over the cork of the bottle: the under side of the cap was attacked by the solvent properties of the wine, and that was why good claret* contained more lead than cheap raw wine, and presumably why vintage port had been left out. If the trade was given some time it might be found that plastic covers could be used instead. Even aluminium would be safer. "I urge the Minister to help us to take action, otherwise I shall almost be compelled to avoid a decent bottle of claret" was his final plea after bringing the bottle of beer, canned fish, and jam into the dock with canned meat and sardines. Two milligrammes of lead a day would ultimately give rise to chronic lead intoxication in most people. If a man ate eight ounces of canned meat he got two milligrammes; two ounces of sardines, one-third of a milligramme; two pints of beer, roughly another milligramme; and with the water he might drink and the air he breathed he had a daily intake of four milligrammes. That was grossly unsafe and poisonous, and the Ministry was showing complacency instead of urgency.

Plastics and Sealing Wax

Mr. W. M. F. VANE, Parliamentary Secretary to the Ministry of Agriculture, Fisheries and Food, said Dr. Stross had left them wondering how it was they were still half-alive. The object of the regulations was to achieve as far as possible the elimination of lead content in food. The general trend was to drop manufacturing processes which had been shown to leave a high content of lead, and to substitute plastic pipes. The regulations represented a big step forward. Water, he explained, was not food within the meaning of the Food and Drugs Acts. Port was a rather special case and was excluded from the schedule, but none the less came under the general regulation imposing a limit of two parts per million. He was taken up by Mr. G. R. MITCHISON (Kettering, Lab.) about lead capsules on bottles, and offered the possibility that in many cellars sealing wax was found just as good. Mr. Mitchison thought this might reasonably be taken up with the wine trade, and Mr. VANE promised to see that representations were made. He defended the general limit of two parts per million, with lower limits, specified for most drinks, to come into operation in two years as desirable to ensure a smooth transition from old to new processes. The motion was withdrawn.

*See also a letter in our Correspondence Columns, p. 1572.

Medico-Legal

MEDICAL EVIDENCE

[FROM OUR LEGAL CORRESPONDENT]

In two recent decisions the Courts have expressed views on the weight to be given to medical evidence.

In one of the cases (White *v.* the Board of Governors of Westminster Hospital and McAuley, *The Times*, October 26) the Court held that when the onus is on one of the parties to an action to prove a certain matter (e.g., the negligence of the defendant) and his medical witnesses do not agree it is not for the Court to resolve the conflict. If the conflict is a material one the Court will simply hold that the party has failed to satisfy the burden of proof laid upon him.

This action was brought on behalf of a boy now aged 15. He had suffered from a convergent squint in his right eye from the age of 8 months. At the age of 5 he had an operation in Ireland for the rectification of the squint, but without marked success. At the age of 9 he was advised, primarily for cosmetic reasons, to undergo a further operation. The right eye gave poor vision and was valuable only as a standby in case disaster befell the left eye. In 1955 a surgeon performed the operation, in the course of which, while cutting the medial rectus muscle with surgical scissors, he cut into the sclera, the choroid, and possibly also the retina. The cut was sutured, but inflammation set in and the eye had eventually to be removed. The cutting of the medial rectus muscle was made more difficult by the scar tissue by which it was attached to the eye after the previous operation. It was disadvantageous to have "tags" of muscle adhering to the globe. The surgeon knew that on a second operation there was a risk of cutting the sclera because it was possible for a fold of the sclera to become trapped in the old scar tissue. In fact, when he pulled the muscle from the globe, he did pull a puckering of the scleral coat so that he cut through a fold of scleral material when he cut the muscle.

Onus of Proof

The onus was upon the plaintiff to prove that, upon those facts, the surgeon had been negligent. To do this he had to show that the surgeon had fallen below the standard of a reasonably competent eye surgeon. The two expert witnesses called by the plaintiff failed to agree on the means whereby the surgeon could have avoided cutting the sclera. The plaintiff thus failed to show the Court that there was a better generally approved method of doing the operation which ought to have been adopted, and the plaintiff's action was dismissed.

This case demonstrates that it is advantageous not only to the standards of reputation of the profession as a whole but also directly to individual practitioners that medical witnesses should not hesitate to give evidence in negligence actions. If only one of the expert witnesses in this trial had given evidence the Court might possibly have received the erroneous impression that there was one generally approved practice which the defendant surgeon had failed to adopt.

Perverse Rejection of Evidence

This conclusion is underlined by the reverse side of the coin, as shown in a criminal appeal (R. *v.* Bailey, *The Times*, October 24) where the Court of Criminal Appeal held that the verdict of a jury which rejected the unanimous undisputed evidence of three doctors was perverse.

Rodney William Bailey, a 17-year-old farm labourer of Pougher Close, Sapcote, appealed against his conviction for murder at Leicester Assizes in May, 1961. The case against him was that, for no known motive, he had brutally beaten a 16-year-old girl to death with an iron bar. The jury rejected the evidence of three doctors supporting a plea of diminished responsibility, although there was no evidence tending to rebut the evidence of those three doctors. The

Court of Criminal Appeal allowed the appeal, substituted a finding of manslaughter on the ground of diminished responsibility, and sentenced the appellant to life imprisonment. The Court stated that although a jury is not bound by what medical witnesses say it must act on evidence, and if there was nothing before the jury to throw doubt on what the medical witnesses said it must be accepted. These observations apply equally to a judge when sitting without a jury, with regard to his duty to make findings of fact.

PROPER FOUNDATION FOR DEFENCE OF AUTOMATISM

[FROM OUR LEGAL CORRESPONDENT]

The House of Lords recently laid down the rule that when a defendant pleads the defence of automatism it is necessary for a "proper foundation" to be laid down by the evidence before the trial judge can leave the defence to the jury. It is not sufficient for the defendant merely to plead automatism without supporting evidence in order to put the prosecution to the task of disproving the possibility of automatism (*Bratty v. Attorney-General for Northern Ireland, Journal,* November 4, p. 1230).

A subsequent case provides an illustration of the sort of evidence which the courts will accept as sufficient "proper foundation" for this purpose (*R. v. Budd, The Times,* November 8). In this case the defendant appealed to the Court of Criminal Appeal against his conviction at Quarter Sessions for dangerous driving and driving while unfit to drive through drink. The court allowed the appeal against conviction for dangerous driving while unfit to drive through drink.

Victim of Concussion

The appellant, William Eric Robert Budd, of Miskin Road, Dartford, Kent, was seen by the police in the early hours of the night driving his car erratically. After stopping him the police found blood on his evening shirt and a heavily blood-stained handkerchief on the floor. The offside wing of the car was damaged. Although it was reasonably certain that the appellant had been involved in a collision there was no evidence of the circumstances of that collision. The appellant was examined by a police doctor, who stated that the appellant was under the influence of drink. At the time of the examination the police doctor knew that on two previous dates the appellant had been the victim of concussion.

As a defence to both charges the appellant relied on the defence that as a result of the collision he was in a state of automatism for the rest of the journey. The Deputy Chairman at Quarter Sessions had directed the jury that the burden rested on the appellant to satisfy them on a balance of probability that automatism had been made out. The judgment of the House of Lords in Bratty's case shortly afterwards made it clear that this was a wrong direction. In Bratty's case the principle was stated that where the defence had laid a proper foundation for the defence of automatism the burden of disproving it rested on the prosecution. The collision which had damaged the car and injured the appellant was a proper foundation for the defence of automatism.

In view of the Deputy Chairman's misdirection, the Court of Criminal Appeal allowed the appeal against conviction for dangerous driving. The appeal against conviction for driving while unfit to drive through drink was dismissed on grounds that the misdirection of automatism could not have affected the direction on driving while unfit to drive through drink. The driving before the collision could not have been affected by automatism.

A revised British Standard Specification for gas washing bottles used in laboratories (B.S. 2461:1961) may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1, price 4s. each, postage extra to non-subscribers.

Universities and Colleges

UNIVERSITY OF EDINBURGH

Mr. W. McD. McQuillon has been appointed Lecturer in the Department of Orthopaedic Surgery.

Dr. Hugh Miller, who resigned from the appointment of Honorary Lecturer in the Department of Public Health and Social Medicine on October 31, 1961, has been appointed a part-time Lecturer in the Department.

Dr. M. H. Draper is to resign from the appointment of Senior Lecturer in the Department of Physiology on April 30, 1962. Colonel J. E. C. Robinson resigned from the appointment of part-time Lecturer in the Department of Public Health and Social Medicine on October 31, 1961.

UNIVERSITY OF LONDON

On October 10, 1961, Dr. C. F. Harris was elected chairman of Convocation for the remainder of the period 1960–4, in succession to Dr. P. Dunsheath, resigned. Dr. Harris has also been elected chairman of the finance and general purposes committee of the Senate for 1961–2, and has been appointed a representative of the University on the board of management of the London School of Hygiene and Tropical Medicine for the three years ending December 31, 1964.

Mr. J. B. Hume has been elected chairman of the Council for External Students for 1961–2.

The following have been nominated for appointment or reappointment as representatives of the University on the governing bodies of the London County Secondary Schools indicated in parentheses: Dr. A. J. M. Reese (Hugh Myddleton); Dr. M. P. W. Godfrey (Sydenham); Dr. S. Gnessen (Brooke House and Mount Pleasant); Mr. St. George B. Delisle Gray (Upton House and Morpeth); Dr. Sybil Yeates (Waverley, Burrage, Church Manorway, and King's Warren); and Dr. H. W. Bunjé (Battersea County).

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *St. Bartholomew's Hospital Medical College,* Mr. J. D. Cambrook (Dental Surgery) and Dr. Peter Story (Clinical Pathology (Haematology)). *Royal Dental Hospital of London School of Dental Surgery,* Mr. F. R. Coffin and Mr. J. N. W. McCagie (Dental Surgery). *Postgraduate Medical School of London,* Dr. A. St. J. Dixon (Medicine). *London Hospital Medical College,* Mr. A. L. T. Easton (Obstetrics and Gynaecology) and Dr. R. M. Mason (Physical Medicine). *Charing Cross Hospital Medical School,* Dr. P. B. S. Fowler and Dr. B. G. Parsons-Smith (Medicine), Mr. W. P. Greening (Surgery), Dr. R. N. Ironside (Medicine (Neurology)), and Dr. P. B. Kunkler (Radiotherapy). *Guy's Hospital Medical School,* Dr. F. L. Ingram (Dental Radiology). *Institute of Neurology,* Dr. W. H. McMenemey (Neuropathology). *St. Mary's Hospital Medical School,* Dr. P. L. Mollison (Pathology (Haematology)). *St. Thomas's Hospital Medical School,* Dr. P. F. D. Naylor (Dermatology). *Institute of Ophthalmology,* Dr. C. M. H. Pedlar (Pathology). *Institute of Diseases of the Chest,* Dr. J. Pepys (Medicine (Clinical Immunology)) and Dr. L. McA. Reid (Morbid Anatomy). *Institute of Dermatology,* Dr. F. Ray Bettley and Dr. H. J. Wallace (Dermatology). Dr. K. D. Bagshawe has been granted probationary recognition as a teacher of medicine at Charing Cross Hospital Medical School for two years from July, 1961.

The Laura de Saliceto Studentship has been awarded to Dr. Maurice Sutton for two years from October, 1961.

The degree of M.D. was awarded to Harold Caplan on October 18, 1961.

The degree of Ph.D. in the Faculty of Medicine was awarded to E. K. Matthews (St. Bartholomew's Hospital Medical College), T. A. Roberts (School of Pharmacy), and S. H. Shehata (Royal Free Hospital School of Medicine) on October 11, 1961.

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1 2 4]E. Q. Archampong, [1 6]C. G. Barnes, [1 6]A. C. Buck, [1 5]Ann G. Creighton, [1 6]Barbara A. Etheridge, [1 5]D. P. Goodwin, [1 3]M. M. Ilahi, [1 4]R. J. M. Irvine, [1 5]Vanessa M. Jones, [1 6]Elizabeth M. Knott, [1 4]J. W. Paterson, [1 3]B. D. Ross, [1 2]D. W. Straughan, [1 3]J. D. Ward, [1 5]B. P. Whitney, K. W. Abel, D. E. Alder, D. A. Alderton, Solange M. M. Amos, T. M. Andrews, B. D. Apthorp, Antonia F. Bagshawe, M. R. Baldwin, R. N. Bale, P. I. Banky, J. P. Barker, A. N. Barnardo, M. J. Barnes, D. M. Barrow, M. T. Barton, S. M. Bass, N. S. Bilkhu, P. G. Bischitz, M. E. Blacklee, A. G. Boohene, G. T. Bowra, A. P. Bray, T. G. J. Brightmore, S. S. Brook, J. K. Brown, M. D. Brown, Rose Buchanan, R. E. Burfoot, T. Buzady, J. H. Chamberlain, M. Chan, J. R. A. Chawner, Sally A. Cherry, Rosalind E. A. Chinnock-Jones, M. J. E. Chorley, P. B. Christian, E. Christopher, Winifred E. Cobbold, T. E. Cochran, J. A. Coden, J. S. H. Cohen, R. Collingwood, G. E. Conn, I. L. Craft, J. C. Crawhall, A. J. Crompton, J. J. L.

Crosby, D. E. B. Davies, J. G. Davies, R. R. Davies, Sarah E. B. Davies, A. J. G. Davis, Carolyn J. Deeks, A. W. Diamond, R. H. Ellis, J. D. R. Evans, C. S. Flowers, G. H. Forman, D. R. Forsdyke, J. D. Fox, G. M. Froggatt, K. G. E. Frohnsdorff, A. M. Gallop, M. George, Susan E. Gooda, A. D. G. Gordon, R. M. Greenwood, O. H. B. Gyde, M. G. Halford, D. L. Hall, R. Hall, Jennifer M. Handley, J. Harris, C. T. Hart, J. E. Haselden, J. E. Hayes, M. J. Henry, Daphne M. Herbert, M. W. Hewson, V. J. M. Hickman, R. A. Hobdell, H. T. Hodnett, C. A. Hood, J. D. Hookway, Gillian R. Hudson, C. J. Hughes, D. M. E. Hughes, G. Hughes, C. J. Hull, Shirley D. Hunter, Elizabeth A. Hutchinson, Christina M. Jenkinson, N. E. Jensen, B. R. Jewell, R. Johnson, J. H. Jones, J. R. L. Jones, M. C. Jones, N. O. Jones, A. G. Karseras, E. P. Kirk, N. J. Knight, Loretta Suet Wan Ko, A. H. I. Lalljee, J. P. Leff, J. M. Leigh, P. D. Lewis, D. E. Lieber, C. D. R. Lightowler, A. J. Lopianowski, J. O. McFarlane, A. F. McGibbon, J. McLaughlan, C. A. McNeill, H. N. Magnani, R. T. Maguire, J. E. Mandeville, A. J. Marengo-Rowe, R. T. H. Marsden, Valerie M. Marvin, A. E. B. Matthews, H. R. Matthews, A. H. Melhuish, A. D. Metten, A. J. Miller, Doreen M. Miller, B. Milroy, S. T. Minto, R. R. N. Molineux, Elspeth A. Morrison, P. J. Mullin, M. J. B. Nicholson, Rosemary R. Norton, J. E. Oliver, Gillian M. Oxenham, W. H. Pagan, R. M. Palmer, R. G. Palmer, P. W. McL. Parker, Elizabeth F. H. Parry, D. McC. Paterson, P. B. Pattison, B. J. D. Peatfield, J. E. Peck, R. L. Pell, C. J. Percival, D. A. Persoff, D. W. Pierce, Penelope J. Pollard, Ann R. T. Pomerance, C. A. Porter, Angela M. Powell, D. L. Powell, B. J. Preston, Eleanor P. Price-Jones, D. I. Prosser, J. P. Pryor, G. P. Rabey, B. J. Radford, H. P. Rang, D. C. Reader, D. E. Rees, Daphne P. Richards, R. G. Richer, J. M. Robertson, M. Sadr, P. R. Salmon, R. H. Salter, C. N. Scott, Gillian Scott, J. G. Scott, G. N. Shephard, Avril M. Sillitoe, M. Silver, Jennifer E. J. Simmonds, Ann M. Sinclair, A. Singh, L. H. Smaje, C. R. Smith, D. T. M. Smith, Sheila K. Smith, Margaret E. Stafford, M. D. Steyn, C. A. Stossel, Glenda K. Swindells, Mary E. Tate, D. M. A. Taylor, J. M. Thistlewood, D. R. Thomas, L. R. Thomas, Brenda M. Thompson, C. J. Toynton, A. M. Tucker, J. McJ. Turnbull, A. J. Tyack, M. F. Tyrrell, R. C. Uren, J. H. Visick, D. A. Vissenga, R. C. Wales, W. A. Wallbank, Barbara Walsh, Jillian M. Wandless, Adrianne Watkins, J. R. Weatherill, Sheila M. J. Webb, D. G. Wells, Ann M. Whitehead, K. G. D. Williams, A. G. Wilson, P. J. Winter, F. K. Wong, S. M. Woolf, D. J. M. Wright, Jane E. Yeo, L. J. F. Youlten, M. Young.

[1]With honours. [2]Distinguished in pathology. [3]Distinguished in medicine. [4]Distinguished in applied pharmacology and therapeutics. [5]Distinguished in surgery. [6]Distinguished in obstetrics and gynaecology.

UNIVERSITY OF BIRMINGHAM

Dr. R. G. Record has been appointed representative of the University on the Warwickshire Local Medical Training Committee.

The title of Director of Graduate Studies in the Faculty of Medicine has been conferred upon Dr. A. G. W. Whitfield, chairman of the Board of Graduate Studies.

The title of University Research Fellow has been conferred upon the following during the tenure of their present awards or appointments or for the periods of their stay in the University: Dr. E. F. Evans, who is undertaking researches in the Department of Physiology supported by a grant from the Nuffield Foundation; and Dr. M. E. Abrams, who holds a Medical Research Council Clinical Research Fellowship, and Dr. I. Sussman, who holds an Isaac Wolfson Travelling Fellowship, both in the Department of Medicine.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on November 7, with the President, Dr. J. D. S. Cameron, in the chair, the following were elected Fellows of the College:

M. Akram, M. Nellen, K. Hazell, P. L. E. Wood, T. Black, A. K. S. Ahmed, S. B. Roy, G. W. Senter, J. R. Fountain, E. M. Donaldson, T. W. G. Kinnear, T. G. Wilson, E. N. Moyes, R. E. Beamish, F. W. A. Turnbull, W. H. Jopling, W. R. M. Alexander, J. McC. Murdoch, A. S. Thambiah, R. E. Church, R. B. Khambatta, J. MacK. Sutherland, J. S. Sodhy, B. R. Hillis, J. B. Gibson, C. Nwokolo, G. R. Tudhope, S. S. Manchanda, A. Slessor, A. P. Trimble, W. Blackwood, J. B. Stanton, J. A. Simpson, T. O. O. Ogunlesi, T. N. MacGregor, W. Sircus, J. D. Sutherland, M. B. Matthews.

The following were elected Members of the College:

F. S. Fiddes, R. H. A. Swain, F. M. Parsons, T. D. V. Lawrie, J. H. G. Brodribb, L. Koadlow, R. J. Moylan-Jones, S. I. Osman, M. K. El-Dars, J. Grover, J. Schneeweiss, J. C. Davies, Isobel H. Grant, H. C. C. Nwankwo, B. Mahton, R. L. Holman, Kim Siong Lim, A. F. Macdonald, A. G. Ironside, M. S. Grewal, K. S. Holmes, S. C. Chakrabortti, K. B. Harveyson, Z. A. Kassir, K. C. Sharma, A. G. Resnekov, R. H. Shah, W. J. Nicholson, S. R. Christopher, D. S. Nurse, S. Chaudhuri, K. E. de S. Karunaratne, V. P. Hajela, Kwan-How Chin, A. Z. Rizavi, P. J. Toghill, M. J. O'Donnell, A. G. M. Campbell, J. E. Williams, S. M. Rosen, I. S. Berg, A. H. Crisp, J. D. M. Richards, Clyde Ying-Chau Wu, N. R. M. Buist, I. C. Crawford, A. A. M. Gibson, J. T. Ireland, R. U. Ahmed, S. Chokroverty, P. C. C. Pitt, P. N. Jha, B. C. Mehta, Riyazuddin, B.Sc., M.B., Myra Chadwick, A. J. Levi, N. T. A. Byam, R. R. Ghose, P. V. Meswani, Beng Keng Chew, Iris M. Duke.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College, held on November 25, 1961, with the President, Mr. Arthur C. H. Bell, in the chair, a tribute was paid to the memory of Sir William Fletcher Shaw, Honorary Fellow, Past President, and co-founder of the College.

Dr. Sreemanta K. Banerjea was appointed to give the William Blair-Bell Memorial Lecture in 1962.

The following were admitted to the Membership:

S. D. Choudhury, P. K. Irani, Wai-Chee Li.

The following have been awarded the Diploma in Obstetrics:

J. L. S. Alexander, W. W. Alderman, C. L. C. Arnold, R. M. Badminton, K. R. Ball, P. R. Bambridge, D. S. Bamford, E. E. Barnard, E. J. Barnett, A. M. Barnie-Adshead, Rachel M. Bartlett, H. K. Basu, C. Bate, P. Beavon, J. M. Beeley, D. P. Beirne, A. D. Bell, C. F. N. Bennett, J. A. G. Benson, G. C. Bentley, E. H. Berman, A. Bertram, B. Bisseru, Zarina T. Biviji, J. H. A. Black, A. G. Bond, Helen D. Bower, K. R. Bowles, Elizabeth M. W. Bradford, J. T. Breen, J. R. Brew, C. C. L. Brewer, T. R. C. Brodie, P. P. Broughton, C. L. Brown, C. M. Brown, Joan M. Brown, R. M. Brown, Anne M. Bruce, T. B. Buchanan, A. L. Buckley, P. F. J. Bunting, D. R. Burcombe, G. M. Burke, J. C. Burn, N. B. Byatt, A. B. Byles, J. M. Cairns, Catherine D. Campbell, P. C. S. Chapman, W. O. Chukudebelu, R. B. Church, F. R. Cianchi, Gillian A. Clarance Heather G. M. Clarke, R. J. Clement, S. V. Clerk, I. Cliffe, J. A. D. Clinch, G. B. Clinton Jones, Diana E. Clough, J. G. Cochrane, P. G. Coffey, M. A. Cole, M. D. Constable, Daphne I. Cook, F. G. Cooper Sheila A. Corrin, C. McK. Corser, D. R. Couchman, A. J. Cox, Patricia L. Crawford, M. J. Critchley, D. Crookenden, W. A. M. Cutting, J. A. Dacre, Sayda Dardiry, J. T. Dawson, J. G. Delier, Ansuya M. Desai, Mary E. Dewar, Girija Dhar, H. Dinnick, R. X. Dixon, P. R. C. Dowse, Charmaine M. D'Souza, A. M. Duthie, M. M. Dutta, D. J. Y. Dyer, N. C. Eccles, J. S. Edmondson, D. G. Evans, V. C. Faber, Rosemary Fairweather, C. G. Falkner, Davnet A. V. Fenton, Cecilia Fernandes, R. F. M. Forward, H. B. Francis, A. G. Fraser, R. M. Fredman, Frances E. Freeman, D. S. Freestone, D. L. Frosgatt, D. Galliford, J. S. Garvin, Asha Gauba, Elizabeth A. Gaze, S. R. Ghosh, I. Ghulam-Mohammad, Marjorie P. Gibson, W. H. Gibson, M. J. Gilbert, G. Gillespie, T. G. Girdwood, S. T. Godwin, J. Goodchild, H. K. Gooding, N. Gordon, G. J. K. Greenlaw, A. W. Grogono, B. H. Grundy, Rashda M. Hamid, K. W. Hancock, C. E. Harley, D. G. Harries, Evelyn W. S. Harris, P. W. R. Harris, B. A. Hasenson, M. J. Haugh, J. N. Haworth, R. J. Haythornthwaite, A. J. Hayward, G. N. Henderson, Ann Henley, Jinatissa Herat, Elizabeth M. Higham, B. Hill, D. I. D. Hodge, Pauline Hollier, Rita J. Hornik, C. E. Horsfall, I. Hosny, Judith A. Houghton, P. J. C. Howe, H. V. Hughes, F. M. Hull, I. A. Hunter, R. F. Hurding, W. R. Hutton, M. T. Inman, M. C. H. Jackson, Edna M. Jacoby, J. R. James, W. H. M. Jewell, R. W. John, L. Johnman, H. H. G. Jones, J. H. Jones, Kanta Kanwar, Moira B. Kelly, P. W. Kershaw, A. Kirby, G. P. Kirkland, G. A. Kohiyar, H. MacG. Kohler, Jill E. Lakins, J. W. Latham, M. P. G. Lawler, R. Layton, R. A. Lee, Hoei-Tjiang Lim, Therese Shook Chin Lim, Nancy G. Lord, I. S. L. Loudon, D. B. Lloyd, Pramila Loghani, A. J. B. Luke, Elisabeth M. Lurring, R. Lush, I. I. Macaulay, A. R. McCutcheon, P. T. MacDonnell, Helen P. McEwan, D. B. McFarlane, T. McGovern, P. J. McGregor, R. W. McIntyre, A. W. McKenzie, C. A. T. McKinney, Marjory G. McK. McKinnon, Eliza McLaughlin, A. C. MacLean, J. D. McLean, M. J. MacLean, H. D. MacLeod, A. L. Macnair, J. G. Madden, M. Malakar, K. C. Marwick, Anita Mascarenhas, R. Mathuranayagam, Florence Maung Maung, T. C. Maver, J. A. Mead, V. V. Mehta, D. S. Meldrum, M. J. Mellor, W. P. Metcalfe, G. T. Millar, Janette Millar, Nityananda Misra, Marie H. H. Mitchell, M. Modell, N. O. Mohammed, J. Monkman, C. J. Morgan, R. H. Morgan, J. R. Morton, P. D. Moylan, J. T. Mucklow, P. Mullick, R. Mulroy, W. Murdoch, M. Myers, Belinda J. Myles, T. G. Nash, J. P. Neasham, J. E. Noakes, D. L. Norris, S. S. O. Nwosu, J. C. Oakley, S. O'Connell, Barbara E. P. Ogden, M. J. Olver, Ma Nan Oo, M. J. Orrell, K. S. Padmanathan, Rosemary F. McL. Page, S. R. Parikh, D. S. Park, I. B. Patel, B. B. Patil, Margaret E. Pawson, Belinda Perry J. R. Perry, E. N. Pickering, I. C. Pitter, M. J. Rashid, Hazel M. Rawlinson, P. S. Razvi, A. F. Richards, D. F. Richards, J. Rivers-Kirby, Anne P. Roberts, E. G. Robertson, I. E. W. Robertson, M. Rohatgi, C. J. Rowland, D. A. W. Sansome, J. S. Seaton, P. R. Seed, B. M. Shah, S. V. Shah, R. Shapiro, L. A. Sherski, B. A. Sides, Shirley K. M. Sinclair, A. G. Slark, J. D. G. Sloss, M. G. Smedley, A. G. L. Smith, G. C. Smith, Margaret H. Smith, N. H. Smith, A. R. Snead, R. B. Somerset, Patricia M. Sonksen, I. Soutar, Joanna South, P. G. Soutter, J. N. Stenhouse, Hilary Stirland, R. A. Stroud, A. G. Strube, J. C. Swann, W. M. Tait, Pauline E. Tan, Colette Taylor, J. P. Telling, D. F. E. Thallon, A. J. Thomas, Edith P. Thomas, E. H. Thomas, I. C. Thomson, S. K. Tiwari, F. E. Tomlinson, Patricia A. M. Tootill, S. D. Turner, Anne M Urquhart, Tara H. Vanarase, Bik-May Wai, Joan M. Wallace, J. B. Warren, W. R. Watkins, Norah Webb, D. P. Wells, P. Wentworth, Myra Wharf, J. E. White, R. G. White, E. I. Williams, M. K. Williams, F. Wills, A. M. Wilson, M. A. Wilson, R. B. Wilson, P. J. Wise, R. A. Wiseman, Cheong Fat Paul Wong, I. H. Y. Wood, R. J. Woodhouse, D. G. Wray.

Vital Statistics

Acute Respiratory Infection in Pembrokeshire

A short account of an outbreak of an acute respiratory infection in parts of Pembrokeshire was given in the *Journal* of November 25 (p. 1442). At that time the virus had not been identified. We are indebted to Dr. D. J. DAVIES, county medical officer of health of Pembrokeshire, for the following additional information: "The extensive outbreak of acute respiratory infection in the county has now been proved to be due to the influenza 'B' virus. The virus has been isolated from nasal secretions of patients, and serological tests, using acute and convalescent samples of sera, have confirmed the diagnosis. The actual strain of the type 'B' virus has not yet been identified. The outbreak is now in the fourth week. In the north and centre of the

county the incidence, particularly among children, has been very high, and experienced general practitioners state that they cannot remember such an explosive and extensive epidemic of influenza locally. The spread to the south of the county has been comparatively slow, and the incidence so far is considerably lower than in the other areas. In general, the illness has not been severe and complications, including otitis media and influenzal pneumonia, have been rare."

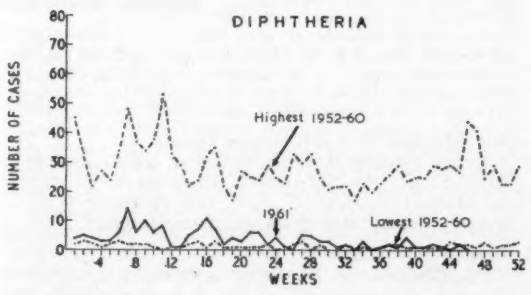
Infectious Diseases

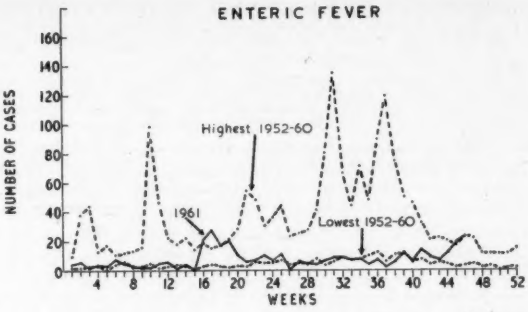
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

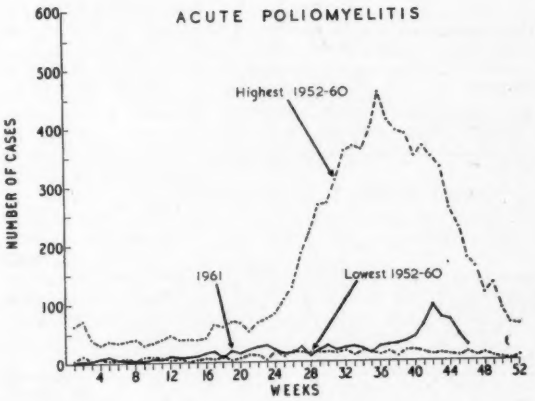
	Week Ending Nov. 18	Week Ending Nov. 25
Acute Poliomyelitis		
Lancashire	5	5
Yorkshire West Riding	5	6
Sheffield C.B.	1	3
Leeds C.B.	0	2
Yorkshire East Riding	1	4
Kingston upon Hull C.B.	1	2
Haltemprice U.D.	0	2
Meningococcal Infections		
Warwickshire	4	10
Birmingham C.B.	4	10
Dysentery		
Berkshire	16	33
Wokingham R.D.	2	30
Essex	29	46
Southend on Sea C.B.	0	20
West Ham C.B.	9	16
Warwickshire	39	43
Coventry C.B.	28	35
Yorkshire West Riding	68	100
Huddersfield C.B.	39	49
Leeds C.B.	13	25
Pontefract M.B.	0	10
Glasgow	145	140
Paratyphoid Fever		
Yorkshire West Riding	0	3
Batley M.B.	0	3
Edinburgh	1	3
Food Poisoning		
Gloucestershire	2	28
Cirencester U.D.	0	21

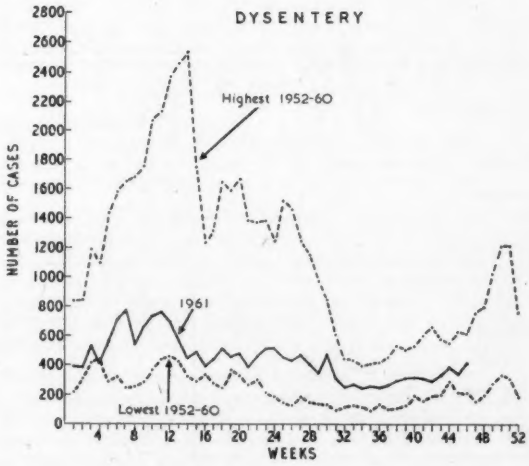
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Industrial Accidents and Diseases

The number of workpeople (other than seamen) in Great Britain whose deaths from accidents in the course of their employment were reported in October, 1961, was 78, compared with 83 in the previous month and 70 in October, 1960.

The numbers of cases of industrial diseases reported during October were as follows: lead poisoning 6, aniline poisoning 1, compressed air illness 2, epitheliomatous ulceration 14, chrome ulceration 7: total 30. There were no deaths.—*Ministry of Labour Gazette*, November, 1961.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 18** (No. 46) and corresponding week 1960.

' Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Engs. & Wales	Lond.	Scot.	N. Ire.	Eire	Engs. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	3	0		2	0	0	0	
Dysentery ..	414	35	245	23	12	492	72	155	2	8
Encephalitis, acute	3	0		0		2	0	0	0	
Enteric fever: Typhoid ..	15	2	0	0		5	0	0	0	
Paratyphoid ..	7	0	0	1		4	0	0	0	
Food-poisoning ..	97	8	8	4		151	41	34	0	
Infective enteritis or diarrhoea under 2 years				10	36				14	28
Measles*	937	33	13	70	145	5,412	302	162	35	68
Meningococcal infection	14	2	8	0		13	0	7	0	2
Ophthalmia neonatorum	16	1	0	0		22	3	1	0	
Pneumonia† ..	179	13	99	1	4	284	18	135	1	
Poliomyelitis, acute: Paralytic ..	21	3	0	} 0		{ 11	4	0	} 0	3
Non-paralytic ..	6	0	3			{ 4	0	0		
Puerperal fever§ ..	143	30	13	0		133	27	12	1	
Scarlet fever ..	413	22	46	16	18	499	32	66	34	27
Tuberculosis: Respiratory ..	339	61	59	16		399	69	70	16	
Non-respiratory	2	15	11	1		56	2	8	1	
Whooping-cough	197	21	30	9	16	1,055	73	101	8	39

DEATHS	1961					1960				
	Engs. & Wales	Lond.	Scot.	N. Ire.	Eire	Engs. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	0		0		1	0		1	
Encephalitis, acute		0			0					0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	1	0	0	6	0	0	2	1
Influenza	18	2	0	0	0	15	0	1	1	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	565	46	25	21	7	540	52	20	11	7
Poliomyelitis, acute	4	1		0	0	0	0		0	0
Scarlet fever ..		1	0	0	0		0	0	0	0
Tuberculosis: Respiratory ..	} 62	{ 3	} 7	{ 1	1	} 73	6	{ 5	1	5
Non-respiratory		1		0	0			0	0	1
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year ..	318	23	23	12	9	318	29	15	11	11
Deaths (excluding stillbirths) ..	10,648	849	674	135	121	10,460	832	617	131	154
LIVE BIRTHS ..	14,749	1270	943	239	354	14,446	1211	907	256	471
STILLBIRTHS .	273	25	21			292	19	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Contraceptive Pill

The Minister of Health announced in Parliament on December 4 that contraceptive pills can be prescribed under the National Health Service. He was replying to a question from Mr. N. RIDLEY (Con., Cirencester and Tewkesbury). The following exchange then took place:

Mr. RIDLEY: Can my right hon. Friend confirm or deny that these pills can cost up to 17s. a month if prescribed? In view of this will the Minister not lay down and publish very careful instructions as to when they may be used, since the prescribing of these pills could cost a lot of money if not controlled on medical grounds?

Mr. POWELL: It is not for me to indicate to doctors what they should decide, for medical reasons, to prescribe for their patients.

Mr. LIPTON (Lab., Brixton): Is it left to the doctor to decide whether these pills shall be prescribed both for married and single women?

Mr. POWELL: It is always for the individual doctor to decide in each case what are the medical requirements.

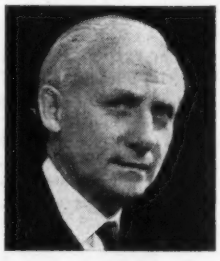
A leading article on the contraceptive pill appeared in the *Journal* of September 16, 1961, p. 754.

Royal Faculty of Physicians and Surgeons of Glasgow

A proposal that the Royal Faculty of Physicians and Surgeons of Glasgow should become a Royal College is at present being considered, said Dr. J. H. WRIGHT, the President, at the Faculty's biennial dinner on December 1. The term "faculty" had come to be regarded as a branch of a university or medical college, and in consequence Fellows of the Royal Faculty had been at a disadvantage in competing for posts with Fellows or Members of other colleges. Furthermore, the absence of the double tier of membership and fellowship had made it impossible for them to have full reciprocity with their sister colleges in medicine. Dr. Wright also announced that Sir HUGH FRASER, an Honorary Fellow, had offered to defray all reasonable expenses in the creation of a new library for the Royal Faculty. The cost, Dr. Wright said, would be about £20,000 or £25,000. (*Glasgow Herald*, December 2.)

Chair of Bacteriology, Westminster Hospital Medical School

Dr. B. W. Lacey, reader in bacteriology at Westminster Hospital Medical School, has been appointed to the newly established chair of bacteriology there from October next year.



Dr. Lacey, who is 48, qualified from Middlesex Hospital Medical School in 1936 and proceeded M.D. in 1954. He joined the staff of the Bland Sutton Institute in 1937. During the war he served in the Army Blood Transfusion Service as pathologist to general hospitals in the Middle East and in 1945 as assistant director of pathology, Middle East Forces, and officer commanding the Central Pathological Laboratory in Cairo. He has been consultant bacteriologist to Westminster Hospital since 1948 and reader in bacteriology since 1952. Dr. Lacey has been particularly interested in whooping-cough, and his published work includes papers on the diagnosis of pertussis, chemotherapeutic synergy, and the influence of environment on the antigenic structure of micro-organisms.

New Members of Royal Society Council

Among the new members elected to the Council of the Royal Society are Sir HAROLD HIMSWORTH, secretary of the Medical Research Council, and Professor W. T. J. MORGAN, deputy director of the Lister Institute.

Hastings Wine Club

The Schoolmasters Wine Club is arranging a tour of the vineyards and places of interest in Southern Spain from

April 7 to 18. The itinerary of the tour, which starts and ends in Madrid, includes Cordoba, Seville, Jerez, Granada, and Toledo. The cost of the round trip from Madrid is £30, but this does not include the journey to and from Madrid from the United Kingdom. Any member of the Hastings Wine Club who would like to join the tour may obtain details from the Honorary Secretary of the Schoolmasters Wine Club either at 188 Brompton Road, London S.W.3 or c/o B.M.A. House, Tavistock Square, London W.C.1.

Heberden Society

The annual dinner of the Heberden Society held in the Fellows' Restaurant at the Zoological Gardens on December 1, with Dr. F. DUDLEY HART, the president, in the chair, was attended by a record number (162) of members and guests. The toast to the Society was proposed by Lord KNOLLYS, who congratulated it on its silver jubilee. After commiserating with its members on the difficulty of raising money for research on rheumatism, he said he was hopefully looking forward to the time when rheumatologists would get all the money they needed. In reply Dr. DUDLEY HART congratulated Professor J. H. Kellgren on being the first worker in Britain to obtain the Gairdner Foundation award. He said the high spot of the Heberden year was the scintillating Heberden Oration given that day by Lord Cohen of Birkenhead, to whom he then presented the Heberden Medal. After Dr. W. S. C. COPEMAN had briefly described the history of the Society from its foundation 25 years ago, two agreeable speeches ended the evening. Dr. A. G. S. HILL proposing the health of the guests, who had as their spokesman the Very Rev. ERIC ABBOTT, Dean of Westminster.

"Enzymologia Biologica et Clinica"

Enzymologia Biologica, a new international journal for biological and medical enzymology, is to be published quarterly. Its languages of publication are English, German, French, Italian, and Spanish. Dr. A. G. EVERSON PEARSE (London) is one of the principal editors, and the editors are Professor Dr. N. DIOGUARDI (Italy), Dr. R. RICHTERICH (Switzerland), and Dr. F. W. SCHMIDT (Germany). The subscription rate for one year is Sw. fr. 56 or U.S. $13.50, and details may be obtained from the publishers, S. Karger S.A., 25 Arnold-Böcklin-Strasse, Basle, Switzerland.

Experimental Eye Research

Experimental Eye Research is a new quarterly journal of which Dr. H. DAVSON (London) and Dr. E. A. BALAZS (Boston) are chief editors. It will publish the results of original research on the anatomy, physiology, biochemistry, and biophysics of the eye. The annual subscription is £5 15s. annually, and details may be obtained from the publishers, Academic Press, 17 Old Queen Street, London S.W.1.

National Association for Maternal and Child Welfare

The National Association for Maternal and Child Welfare has issued a leaflet, *Neo-Natal Cold Injury,* which gives warning of the striking and deceptive redness of cheeks and extremities in newborn babies suffering from severe chilling. Copies may be obtained from Comatchwel Ltd., at the National Association's address: Tavistock House North, Tavistock Square, London W.C.1. (Single copies cost 9d. each, post free; bulk orders £2 10s. per 100, or £21 per 1,000, plus carriage at cost.)

Ministry of Health Building Notes

Guidance on the design of training schools for nurses is given in No. 14, the latest in the series of the Ministry of Health Building Notes (H.M.S.O., price 1s. 6d. net). Costs are dealt with in a loose-leaf sheet issued as an addendum to Hospital Building Note No. 2, *The Cost of Hospital Buildings.* The cost allowances set out are related to the number of places provided—for example, for the first 100 student nurse places the allowance is £23,500, with £88 for each additional place.

Invalid Children's Aid Association

At the annual general meeting of the Invalid Children's Aid Association held on November 21 the chairman, Mr. W. E. WALLACE, referred to the developing work of the I.C.A.A. and particularly the building of a new wing at Pilgrims School, Seaford, for the care largely of asthmatic boys, to which the Wolfson Foundation had contributed £20.000. Dr. A. WHITE FRANKLIN paid tribute to the Buttle Trust, whose generous grant had allowed the I.C.A.A. to start house-hunting for a new home and school for children without speech, and said that perhaps the most exciting new project was the establishing of a combined casework unit to be set up in London for workers from the Invalid Children's Aid Association, the Family Welfare Association, and the Family Service Units. This was being made possible by a grant from the London Parochial Charities of £60,000 to be spread over five years.

News from Australia

▶ The annual report of the Royal Flying Doctor Service says that in the last year the service's planes made 1,500 flights and its bases provided 11,000 medical consultations by radio. The service was used during the year by 800 white patients and 500 aborigines and cost £A.250.000. It has recently expanded its work by providing regular dental treatment for the inhabitants of the remote Furneaux Islands in Bass Strait.

▶ The Australian Health and Medical Research Council has recommended that public authorities throughout Australia should add fluorine to their water supplies to help reduce dental decay.

▶ The Australian Health and Medical Research Council has asked its nutrition committee to report on the desirability or otherwise of uniform State and Federal action to restrict the sale of vitamins.

Presentation to Sir John Boyd

Pathologists who served in the M.E.F. and C.M.F. are holding a reunion dinner in London on January 4. Sir JOHN BOYD, F.R.S., will be the guest of honour and it is hoped to make a presentation to him at a later date. Those who would like to be associated with this gift should communicate with Professor G. J. CUNNINGHAM, Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2.

Royal Society of Health

Dr. J. GALLOWAY, Wolverhampton's Medical Officer of Health, is to be chairman of the council of the Royal Society of Health from January 1.

Queen Mary's (Roehampton) Hospital Transfer

The administration of Queen Mary's (Roehampton) Hospital, which since 1953 has been administered directly by the Ministry of Health, was transferred to the Board of Governors of Westminster Hospital on December 1. The administration of the Limb-fitting Centre will remain the responsibility of the Ministry.

Professions Supplementary to Medicine

The Registrar of the Council for Professions Supplementary to Medicine, Mr. J. S. TAPSFIELD, took up his appointment on December 1. The address of the Council is St. Luke's Hospital, Sydney Street, London S.W.3.

Royal College of Physicians of Edinburgh

Dr. J. D. S. CAMERON has been re-elected President of the Royal College of Physicians of Edinburgh.

Industrial Injuries Advisory Council

The following are among those appointed or reappointed to the Industrial Injuries Advisory Council for the new term which began on November 30: Professor R. E. LANE, Mr. S. A. S. MALKIN, Dr. D. G. MORGAN, Dr. L. G. NORMAN, Dr. ALICE M. STEWART.* (*New appointment.)

In Brief

An abstract mural painting by William Scott which is to be placed in the entrance hall at the Altnagelvin Hospital

in Londonderry will be on exhibition for a few weeks at the Tate Gallery. The mural, 46 feet long and 9 feet high, is painted on 15 panels.

Schofield Hall, a £25,000 extension to the headquarters of the Manchester Institute for the Deaf, was officially opened on November 22.

People in the News

▶ Professor A. C. FRAZER, professor of medical biochemistry and pharmacology at the University of Birmingham, has been appointed chairman of a commission to advise the East African Governments on the future financing and administration of research in their territories in medicine and natural resources.

▶ Dr. J. F. WILKINSON, director of the Department of Haematology at the University of Manchester, has been elected a president of the European Haematological Society.

▶ Mr. B. N. BROOKE, reader in surgery at the University of Birmingham, has been awarded the Graham award for 1961 of the American Proctologic Society for his work on non-malignant ulcerative disease of the colon.

COMING EVENTS

Royal College of Surgeons of Edinburgh.—Professor A. W. WILKINSON, "Some Surgical Aspects of Neonatal Homoeostasis," December 8, 3.30 p.m., in hall of College.

Chest and Heart Association.—Symposium, "Modern Views on the Diagnosis and Management of 'Stroke' Illnesses," January 23, 3.30–7.30 p.m., Barnes Hall, Royal Society of Medicine, 1 Wimpole Street, London W.1. Chairman: Sir RUSSELL BRAIN. Details from C.H.A., Tavistock House North, Tavistock Square, London W.C.1.

Central Council for Health Education.—Annual conference, "Parents and Children," January 25, 10 a.m.–4 p.m., National Film Theatre. Details from Medical Director, C.C.H.E., Tavistock House North, Tavistock Square, London W.C.1.

NEW ISSUES OF SPECIALIST JOURNALS

*The Journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.*1.

THORAX

A Clinical Evaluation of the Rygg-Kyvsgaard III and the Mark III Pump Oxygenators. E. Arnfred, Inge H. Rygg, Torkild Frederiksen, H. C. Engell, Thue Poulsen, and J. Rosen.
A Technique for the Combination of Profound Hypothermia and Extracorporeal Circulation with Complete Circulatory Arrest. A. J. Gunning.
The Technique of Hypothermic Perfusion. P. J. Molloy and R. I. Lindfield.
The Results and Complications of Hypothermic Perfusion. P. J. Molloy.
Surgical Correction of Coarctation of the Aorta by an "Isthmusplastic" Operation. K. Vossschulte.
The Surgical Treatment of the Tetralogy of Fallot. C. N. Barnard and V. Schrire.
Haemolytic Anaemia of Mechanical Origin after Open Heart Surgery. H. M. Sayed, J. V. Dacie, D. A. Handley, S. M. Lewis, and W. P. Cleland.
The Streptomycin Concentration in Tuberculous Cavities. K. D. Arosenius, V. O. Björk, and G. Laurell.
Multiple Pulmonary Artery Aneurysms. Robert W. Charlton and Louis A. Du Plessis.
Rheumatoid Pneumoconiosis (Caplan's Syndrome) in an Asbestos Worker. W. G. Tellesson.
Myelomatosis with Extensive Pulmonary Involvement. Zelman Freeman.
Tracheopathia Osteoplastica. R. Salm.
Failure of Sternal Fusion with Herniation of the Pericardium. H. T. Thompson.
Acute Disseminated Histoplasmosis of Pulmonary Origin Probably Contracted in Britain. A. A. Miller, F. Ramsden, and M. R. Geake.
An Unusual Case of Haemoptysis. F. J. Clark.
Proceedings of the Thoracic Society.
Index.

Volume 16, No. 4. (Quarterly ; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, December 11

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. F. Goodwin: Pulmonary Vascular Disorders.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Edridge-Green Lecture by Sir Wilfrid E. le Gros Clark, F.R.S.: Sorting Principle in Sensory Analysis as Illustrated by the Visual Pathways.

Tuesday, December 12

ASSOCIATION OF ANAESTHETISTS OF EDINBURGH.—At Royal College of Surgeons of Edinburgh, 7.45 for 8 p.m., Mr. F. J. Gillingham, Mr. McCormack, Mr. McNair, and Mr. J. Scott: Care of Patients with Multiple Injuries.

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. J. Michael Jefferson: Thrombosis of the Anterior Cerebral Artery.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. I. D. P. Wootton: Retention of Aromatic Compounds in Acute Renal Failure.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Dr. N. Compston: Megaloblastic Anaemias.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5.30 p.m., Harben Lecture by Sir Christopher H. Andrewes, F.R.S.: The Common Cold—(1) Background.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. Aleck Bourne: Amenorrhoea, its Causes and Significance.

Wednesday, December 13

FOUNTAIN HOSPITAL.—5.30 p.m., Dr. K. Bobath: Problems of Treatment of Patients with Cerebral Palsy and Mental Subnormality.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. H. Nicholson: Early Diagnosis of Bronchial Carcinoma.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. M. Wallace: Cancer of the Bladder.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Manchester University Medical School, 4.30 for 5 p.m., Dr. J. O. Tobin: Live or Dead Poliomyelitis Vaccines?

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. W. W. Payne: Biochemistry in the Newborn.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. I. Friedmann: Electron Microscopy.

ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Dr. R. A. Womersley: Magnesium Metabolism.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5.30 p.m., Harben Lecture by Sir Christopher H. Andrewes, F.R.S.: The Common Cold—(2) Recent Laboratory Work.

SOCIETY OF CHEMICAL INDUSTRY: NUTRITION PANEL.—At 14 Belgrave Square, London S.W., 6.15 p.m., subject: Foods Low in Carbohydrate. Papers by Professor W. J. H. Butterfield and Mr. A. F. Jackson and Dr. G. R. Howat. Ph D., F.R.I.C.

Thursday, December 14

BRISTOL UNIVERSITY: DEPARTMENT OF PSYCHIATRY.—At Large Theatre, Queen's Building, University Walk, 8.30 p.m., Mr. H. Gwynne Jones, B.Sc.: Behaviourist Approach to Neurosis and its Treatment.

BROOK GENERAL HOSPITAL.—5.45 p.m., Dr. C. L. Joiner: Nephrotic Syndrome.

CAMBRIDGE MEDICAL SOCIETY.—At Audit Room, King's College, Cambridge, 8.30 p.m., Professor J. D. Boyd: Vesalius.

INSTITUTE OF CHILD HEALTH.—5.30 p.m., Dr. Alvar Swensson (Stockholm): Respirator Treatment for Children.

LIVERPOOL MEDICAL INSTITUTION.—6 p.m., Christmas cocktail party.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Robert Jones Lecture by Mr. William Gissane: Basic Surgery of Major Injuries of the Motorways.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5.30 p.m., Harben Lecture by Sir Christopher H. Andrewes, F.R.S.: The Common Cold—(3) Epidemiology and Possibilities of Control.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., Dr. F. I. C. Apted: Sleeping Sickness in Tanganyika: Past, Present, and Future. A discussion will follow.

Friday, December 15

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.

KEIGHLEY AND DISTRICT MEDICAL SOCIETY.—At Keighley and District Victoria Hospital, 8.30 p.m., Mr. R. M. Gibson and Dr. D. Taverner: The Stroke Syndrome.

Saturday, December 16

BIOCHEMICAL SOCIETY.—At Wolfson Institute, Postgraduate Medical School of London, 10.30 a.m., 411th meeting.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Colston.—On November 25, 1961, in Birmingham, to Enid (formerly Furnival) and Dr. Brian Colston, a daughter—Lucy Brigid.
Connell.—On November 22, 1961, at R.A.F. Hospital, Norton Hall, Lincolnshire, to Joan M. Connell (formerly Whitham), M.B., B.Chir., D.P.M., and J. W. M. Connell, a brother for Michael, Caroline, and Patricia—Delmond Norman John.
Oliver.—On October 31, 1961, to Drs. Margaret (formerly Abbey) and Micael Oliver, of East Morningside House, Edinburgh, a brother for John, Sarah, and Mark—Paul James Yool.
Shindler.—On November 24, 1961, to Dr. Elizabeth (formerly Korn) and Stanley Shindler, a daughter—Penelope Anne.

DEATHS

Coad.—On November 19, 1961, Stanley Allan Coad, M.R.C.S., L.R.C.P., of the Nightingales, Southborough, Kent, aged 91.
Gillespie-Hill.—On November 17, 1961, at King Edward VIIth Hospital, Windsor, Rachel Noeleen Gillespie-Hill, M.R.C.S., L.R.C.P., of Wraysbury House, Wraysbury, Bucks
Judah.—On November 14, 1961, at Bombay, India, David Judah, M.D., aged 81.
Mackay.—On November 18, 1961, Charles Mackay, M.B., Ch.B., D.P.H., D.T.M., of Hill Rise, Winterbourne Road, Teignmouth, Devon.
Mayberry.—On November 21, 1961, at Greenlane, Riverhall Hill, Frant, Sussex, George Mayberry, L.R.C.P.I., aged 78.
Osborn.—On November 20, 1961, at Ipswich Nursing Home, Sidney Osborn, M.B., Ch.B., L.D.S. R.C.S., of 61 Henley Road, Ipswich, Suffolk, aged 72.
O'Shea.—On August 30, 1961, Patrick O'Shea, M.B., B.Ch., Lieutenant-Colonel, R.A.M.C., retired.
Taylor.—On November 22, 1961, at Bath Nursing Home, Stuart Hopcraft Stanley Taylor, M.B., Ch.B., of 10 Edward Street, Bathwick, Bath.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Paramethadione During Pregnancy

Q.—*A girl aged 21 has been taking paramethadione 0.3 g. twice daily for 12 years for petit mal. There have been no toxic effects. She is about to be married. Would paramethadione in this dosage, necessary to control the attacks, affect the foetus should she become pregnant?*

A.—On the whole it is improbable that continuation of therapy in this case would have any effect on the foetus should the patient become pregnant. The pharmacological action of both troxidone and paramethadione is extremely specific for the suppression of petit mal attacks, and apart from mild sedative and analgesic activity they have no other significant effects. As the patient has been taking the drug for such a long time without experiencing any of the serious toxic effects, blood dyscrasias, renal damage, skin rashes, etc., which sometimes follow therapy with the diones it is extremely unlikely that anything untoward will occur now, but the development of pregnancy is occasionally followed by an altered sensitivity to a drug which the patient has previously been taking without any trouble.

Spanish Haemostatic

Q.—*A patient whose duodenal ulcer bled while on holiday in Spain returned with some ampoules of "quercetol hemostatico" for intramuscular injection which contained ingredients as set out in the following formula: "Quercetina 0.005 g.; semicarbazona de N-metil-2 : 3-dihidro-3-hidroxi-5 : 6-quinona-indol. 0.0025 g.; sulfato doble de creatinina y 5-hidroxi-triptamine 0.0025 g.; solucion esteril c.s.h. 3 cc." This was supposed to increase the coagulability of the blood. Have any of these substances a haemostatic action when injected?*

A.—This preparation is an example of undesirable polypharmacy. While I am not familiar with all the ingredients of this intramuscular cocktail, at least two of the substances mentioned have some claim to be considered as haemostatic agents. Quercetine is a substance allied to the more familiar rutin or hesperidin drugs which are claimed to have an effect on capillary permeability and to be capable of restoring it to normal in cases where there is a deficiency of the so-called vitamin P. The existence of this vitamin and still more of any disorder due to the lack of it is in considerable doubt. 5-Hydroxytryptamine (serotonin) has possibly some role to play along with the blood platelets in the complex processes of blood coagulation, but it has not been proved that deficiency of this substance is accompanied by any haemorrhagic tendency. It is extremely unlikely that any of the substances in this preparation, particularly in such minute doses, would have any effect upon the coagulability of the blood or upon the tendency of the patient to bleed.

Deodorant Powders

Q.—*What are the active agents in deodorant powders and hair-removing creams? Are such preparations harmful with repeated use?*

A.—Deodorant powders owe their effectiveness principally to the suppression of sweating. For this purpose aluminium salts are those chiefly used. These powders therefore consist of a vehicle of talc, starch, or similar inert powder with the addition of a small proportion of the aluminium salt. There is some evidence that an effective application is accompanied by a slight inflammatory response, and these powders should therefore be used with reasonable caution. There is evidence also that body odour results from bacterial action upon sweat and not from sweat alone in its pure state. This has led to the use of antiseptics or bacteriostatics for this purpose, but they are not usually incorporated in powders. Hair-removing creams contain either sulphides, particularly strontium sulphide, or mercaptans, particularly thioglycollate.

Both deodorants and hair-removing creams are capable of irritating the skin if they are used unwisely. Depilatory creams particularly should not be left on the skin too long. In ordinary dermatological practice, however, it is quite unusual to see any damage, even temporary, resulting from the use of these preparations. There is no cumulative effect, so that repeated use is no more dangerous than occasional.

Long-term Value of Oral Hypoglycaemic Agents

Q.—*A woman diabetic aged 57 has been stabilized on a dose of chlorpropamide 100 mg. daily, and her urine tests are consistently blue. She has a diabetic retinopathy, and I am anxious that the change of treatment to chlorpropamide should not result in long-term deterioration as compared with insulin. Can you give me any idea of the comparative long-term effects?*

A.—It is not yet possible to compare the long-term effects of oral hypoglycaemic agents with those of insulin, because the former drugs have been in use only for a limited time. Any deterioration in the retinopathy would not necessarily be attributable to chlorpropamide, since this may occur in spite of apparently adequate control of the diabetes. Nevertheless, it would be advisable to watch carefully for a return of symptoms and to continue testing evening and early-morning specimens of urine for sugar, because resistance to chlorpropamide may appear months or years after initiation of treatment. If an increase in dosage does not control the glycosuria then insulin will have to be substituted.

Premenstrual Mastalgia

Q.—*Is there any effective treatment for painful lumps in the breasts which enlarge premenstrually? I believe dimethyl stilboestrol and progesterone have both been used in this condition, and would be grateful for information about the dosage employed. Is this condition still regarded as being due to an increased oestrogen–progesterone ratio, and is it precancerous?*

A.—Slight discomfort and enlargement of the breasts before each period are normal physiological reactions. When they are exaggerated to form what is sometimes called premenstrual mastalgia it is regarded as part of the menstrual tension syndrome. The pain, and even perhaps the lumpiness of the breasts, is probably caused by oedema of the interglandular tissues which is a manifestation of generalized fluid retention. This is said to be related to an excessive oestrogen or a diminished progesterone action, but it is remarkable that premenstrual mastalgia is a feature of ovular rather than anovular menstrual cycles. Like premenstrual tension in general, this complaint invariably has an important background of over-anxiety and mental stress. Cancerophobia is often present when symptoms are directed mainly to the breasts.

Various forms of hormone therapy have been advised, but none is very satisfactory. Oestrogens are contraindicated, but a progestogen such as ethisterone, 10 mg. three times daily for 7–10 days before each period, may be tried and can do no harm. Stronger progestogens are likely to disturb the menstrual cycle. Methyl testosterone, 5–10 mg. sublingually daily during the second half of the cycle, usually suppresses the breast activity but cannot be used indefinitely because of virilizing side-effects. Indeed, hormone therapy should be avoided in these cases if possible. The first requirements are reassurance and advice to avoid handling the breasts and searching for nodules. Correction of the background causing nervous tension is also important. The

patient can usually control her symptoms to a considerable extent by severely restricting her intake of fluid and salt for 7 to 10 days premenstrually. Failing this a diuretic such as ammonium chloride or chlorothiazide can be given during the few days when the discomfort is expected.

Premenstrual mastalgia is not precancerous. Only when the breasts show true chronic cystic hyperplasic mastitis, characterized by fibroadenosis and epithelial hyperplasia, is there an increased risk of subsequent carcinoma.

Fluoride and the Brain

Q.—*Has sodium fluoride any sedative or narcotic action, and, if so, would fluoridation of drinking-water to the extent of one part per million be likely to have any effect?*

A.—There is no evidence that the fluoride ion has any pharmacological action on the brain. When the daily intake of fluoride is small (up to 5 mg.) excretion is complete and storage in the body does not occur. When larger amounts are taken storage takes place mainly in the bones and teeth. A concentration of fluoride ion of one part per million in the drinking-water has not been shown to have any significant harmful effects. In some communities the natural content of fluoride in the drinking-water is greater than this, and apart from mottling of the dental enamel no injurious effects have been noted.

Cobalt Bomb

Q.—*When and where was the cobalt bomb first used in the treatment of cancer? Are any other elements used in "bomb" form for the same purpose?*

A.—The first teletherapy cobalt unit was installed in the hospital at Saskatoon in Saskatchewan in August, 1951. By the beginning of 1960 there were 700 cobalt units in 44 countries. The first cobalt unit in this country was installed at Mount Vernon Hospital, Northwood, and the first treatment was given there on March 1, 1954 (it was installed six months before this). Other elements used in "bomb" form are radium (now outmoded), caesium-137, and iridium.

Agranulocytosis from Phenylbutazone

Q.—*What is the relative likelihood of agranulocytosis if phenylbutazone is given in a dosage of 200 mg. or 300 mg. daily for prolonged periods?*

A.—Phenylbutazone is now well recognized as a drug which occasionally causes agranulocytosis and other blood dyscrasias. The total number of cases reported, however, is small, and many physicians who have used the drug extensively have not met this toxic effect. Hart and Burley,[1] for example, state that they have used phenylbutazone regularly since 1952 in a dosage of 300–400 mg. daily and have not had a single case of agranulocytosis. It is difficult to give any accurate numerical estimate of the likelihood of agranulocytosis because very few reports give the total number of patients who have received the drug. In 1953 Leonard[2] reported 11 instances out of 1,526 patients receiving phenylbutazone, but the overall incidence of agranulocytosis is certainly not as high as these figures suggest. In 1955 Mauer[3] found only 25 cases, 10 of them fatal, in the world literature. In Denmark from 1951 to 1957 there were 65 fatal cases of agranulocytosis; of these, 25 were attributed to drugs and only 2 of these to phenylbutazone.[4] In England and Wales in 1958 there were 8 "fatal therapeutic misadventures" attributed to phenylbutazone; 5 were due to phenylbutazone alone and 3 to its use in combination with other drugs.[5] Probably not all these deaths were due to agranulocytosis, since other fatal hypersensitivity reactions can be caused by phenylbutazone.[6] In general terms it is true to say that there is not a direct relationship between either the daily dose or the total amount of phenylbutazone given and the occurrence of agranulocytosis. It has occurred with a daily dose as small as 400 mg. and after a total dose of only 3.5 g.[7] In the majority of reported cases the agranulocytosis has appeared soon after the onset of a course of treatment, usually within 10 to 60 days, and serious toxic reactions are very rare after prolonged periods of administration. Mason and Steinberg,[7] for example, reported their experience with 315 patients who were treated for at least four years on an average maintenance dose of 300 mg. daily. None of their patients developed a blood dyscrasia.

REFERENCES

1 Hart, F. D., and Burley, D., *Brit. med. J.*, 1959, **1**, 1087.
2 Leonard, J. C., ibid., 1953, **1**, 1311.
3 Mauer, E. F., *New Engl. J. Med.*, 1955, **253**, 404.
4 Mosbech, J., and Riis, P., *Acta med. scand.*, 1960, **166**, 343.
5 *Registrar-General's Statistical Review for England and Wales for 1958. Part III. Commentary*, 1960. H.M.S.O., London.
6 Fraser, T. N., *Brit. med. J.*, 1955, **1**, 1318.
7 Mason, R. M., and Steinberg, V. L., ibid., 1960, **2**, 828.

NOTES AND COMMENTS

First-aid Book for Laymen.—Dr. J. T. HAYWARD-BUTT (Phoenix, Arizona) writes: It would seem to me that your questioner might derive value from a small book, *First Aid Illustrated*, written by my father, Dr. H. T. Hayward-Butt, for just such occasions as he envisages. This soft-cover, pocket-size booklet was written, mainly for first-aid workers of limited education, for the mines and industrial areas of South Africa. It is almost entirely pictorial, with a short text in relatively simple language explaining each photograph. It covers the whole field of trauma and fractures from spinal injuries to Colles fractures and concentrates on what an intelligent layman can do for these in the way of transport, splinting, bandaging, and anti-shock care in the absence of skilled medical attention. The booklet is now in its 13th edition and has been translated into 12 languages, though the pictorial presentation is such that the text is almost superfluous. The book is published by Longmans, Green and Co. Ltd., London (price 4s.).

Vaccination Sites.—Dr. C. HUNTER-SMITH (Dover) writes: I have been vaccinating babies on the sole of the foot for over 14 years. The question is raised again in "Any Questions?" (November 18, p. 1375). I have used this site only for girls at pre-toddler age. I agree with the finding that reactions local and general are apt to be more severe when this site is used, but I have never had an excessively severe reaction, and as the scar is entirely unnoticeable I think the method is worth while. I used this site to vaccinate both my daughters. Of course some of my unblemished arms are now being marked by B.C.G. vaccination.

OUR EXPERT replies: It is, of course, possible to vaccinate large numbers of children of pre-toddler age safely on the sole of the foot, especially when home conditions and after-treatment are satisfactory. If one is asked for advice as to the safest method to adopt in all sorts and conditions of infants over a long period of time it is felt that it is wise to recommend the upper arm. It is a matter which must naturally be decided by every doctor, having regard to home conditions and the type of parent.

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The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

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Any Questions?, Volume 3 (8s. 3d.).

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